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From the Tuberculosis Department, 20th District Child Hospital, Budapest (Head: Dr. Stefen Simkó)

The Use of Hibernation in the Bronchoscopic Examination of Infants and Children

by Z. LÁBAS and S. SIMKÓ

In general, there are three methods of bronchoscopy in the pediatric practice: that with no anaesthesia, that with local anaesthesia and finally that with general anaesthesia.

The followers of Jackson's school think that the use of anaesthesia is unnecessary under the age of 6 years. It is beyond doubt that bronchoscopy without anaesthesia requires a highly skilled bronchologist, but even then it exposes both the patient and the assistants to great strain. Most children will in fact become restless, will begin to cry, shout and fight when strapped to the operating table, or when the mouth gag is put in place and will resist any medical interference. Thus, bronchoscopy is not easy to carry out. The desperate resistance of the child will further increase when the bronchoscopy tube is inserted into the hypopharynx and the radix of the tongue is raised, and the result is a laryngospasm and an increased tension in almost every muscle of the body. Only the inspiration will force the child to open the glottis for a very short time. If the glottis cannot be visualized immediately in the bronchoscopy tube, and especially in cases where saliva, secretion or a thick tongue root interfere with orientation, it may take several minutes before even the most experienced bronchologist can find the glottis. Moreover it is just with children that the rapidity of examination is of paramount importance. Prolonged examination will actually increase the chances of causing injury to hypopharynx-larynx, trachea and bronchi, to the mucosa or other tissues. Such trauma may in turn lead to apnea, shock or subglottic edema. When no anaesthesia is employed, retching, or above one year of age violent coughing, may interfere with examination in many cases. The discomfort caused by the introduction of the tube may cause psychical trauma, a factor not to be ignored in children weakened by tuberculosis, asthma, or other diseases. Experience has shown us that

premedication with barbiturates and atropine does not ensure an undisturbed medical examination.

Local anaesthesia may be employed with reasonable security only in children older than 6 years. In younger patients technical difficulties make the procedure so complicated that the stress caused by it almost equals that caused by bronchoscopy. The high toxicity of the compounds used for mucosal anaesthesia should be borne in mind too.

No form of inhalation or intravenous anaesthesia is without danger, which may be too great to justify the use of such procedure in a diagnostic method. Ether has the disadvantage of causing a suffocating sensation, ample secretion and irritation of the respiratory tract. Previously administered atropine will usually fail completely to overcome the irritative effect.

In the past we carried out bronchoscopy without anaesthesia on children under the age of 6 years. Recently, however, impressed by the results achieved by the use of hibernation in surgery and medicine, attempts have been made to employ this method as a preliminary procedure to bronchoscopic examination. The solution used for inducing hibernation was the "cocktail lytique" recommended by LABORIT and HUGUENARD, containing 1 mg largactil, 1 mg phenergan and 2 mg dolargan (dolantine) in each ml. The dose was 1 ml/kg body weight, given intravenously. In some cases one single injection sufficed, but in others the effect was not satisfactory, sleep being too light to make smooth bronchoscopic examination possible. In such cases another dose, this time $\frac{1}{2}$ ml/kg, is injected intravenously 20 minutes later. In the presence of technical difficulties the solution may be injected intramuscularly, in combination with hyaluronidase. If so required, the dose may be repeated 20 minutes later even 5 times more. From what has been elaborated above it follows that dosage is highly individual. The only preparation to hibernation is fasting for a few hours. No other drug acting on the nervous system (e.g. barbital, atropine,) is given. The children usually wake within 2 to 4 hours, but the impairment of sensorium and deconnection are not abolished until 10 to 12 hours later. Wakening is smooth, uneventful, after-pain and discomfort are absent.

We have employed hibernation for bronchoscopy in 150 cases. The experience obtained may be summed up as follows:—

When given the doses specified above, the children usually fight against the injection only and by the time the needle is removed, or sooner, they are quiet, cease crying and sleep lightly (narcobiotic sleep). The dose of the "cocktail" is such that temperature, pulse, respiratory rate and blood pressure are not substantially altered. After the desired effect developed, the patient under narcosis is placed on the operating table. Although the

legs are strapped to the table and the shoulders are held by an assistant, these are precautions, rather than necessities, because the children do not struggle and show only minimal resistance (combined analgesic, sedative, narcotic and relaxant effect). Reduction in muscle tone (relaxant effect) results, which contributes greatly to the elimination of struggling, laryngospasm or other disturbing muscle activity, so common otherwise when the bronchoscope is being introduced. We attribute great importance to the amnesia following bronchoscopic examination and to the absence of psychical trauma (fear, anxiety, etc.), of the sensation of suffocation and respiratory depression, the untoward complications so frequently seen when other methods of anaesthesia are employed.

Hibernation and intravenous anaesthesia are different in pharmacological action and the former is far less dangerous. As the phenothiazine derivatives have but a slight narcotizing effect on the cells of the cerebral cortex, and act mainly by interrupting the connection between brain-stem and cortex (conduction blockade), sleep is not deep and only certain reflexes are extinguished. For example, the emetic reflex is absent (antiemetic, chiefly largactil effect), but a diminished coughing reflex is present, this being advantageous from the point of view of the bronchologist. Deconnection also abolishes the exaggerated vegetative reflex sensitivity, thereby eliminating errors in regulation that may result from bronchoscopy and may interfere with respiration, blood pressure and heart function (shock effect). Another advantage is the diminution of bronchial secretion (parasympathetic inhibition). The antihistamine effect, mainly of phenergan, may play an important role in the prevention of subglottic edema.

The advantages of hibernation, as used at bronchoscopic examination, may be summarized as follows:

1. The patient is not exposed to undue discomfort.
2. It can be carried out at any age.
3. The bronchologist can work without interference since the patient does not move or vomit, secretion is slight, etc.
4. It is easier to introduce the bronchoscope.
5. Owing to quiet work, the duration of examination is shortened.
6. Injury that may be caused by the bronchoscope is reduced to a minimum.
7. The probability of subglottic edema is greatly diminished.
8. Vegetative reflex hypersensitivity is substantially decreased by the prevention of shock and of apnea.
9. The almost total amnesia eliminates psychical alterations connected with bronchoscopy such as fear, anxiety, etc.; this is of particular importance when examination is to be repeated several times.

The aforementioned advantages undoubtedly exist, yet eventual complications should also be borne in mind. For example, even when hibernation lasts but a few hours—there being no reason why it whould be kept up longer with bronchoscopy—conscientious medical attention and care, as well as certain experience are required. It cannot be employed on an outpatient basis, just like bronchoscopy without hibernation under the age of 6 years. Phenothiazine derivatives and dolargan are rather dangerous, although the rather wide range between the toxic and the therapeutic dose eliminates the danger of poisoning with a reasonable degree of certainty when the doses specified are employed. A greater reduction of body temperature, fall in blood pressure, a major loss of K, and respiratory paralysis are not common, but such complications *may* occur and therefore it is essential to control continuously pulse rate, respiratory rate, blood pressure and heart action. The patient must not sit up, as an orthostatic collapse may develop, and the head should therefore be kept low when the child is being transferred from the operating table back to the bed.

From what has been outlined above it follows that hibernation offers obvious advantages over other methods used in bronchoscopic examination of children. When the rules outlined are adhered to, hibernation is dangerous to such a small extent, that it is almost unnecessary now to carry out bronchoscopic examination without anaesthesia in even the youngest child.

Summary

A detailed account is given of the experience from the use of hibernation in the bronchoscopic examination of infants and children, aged from 0 to 6 years. After analysing the favourable features of the pharmacological effect of hibernation in some detail, the potential complications are dealt with. An appraisal of advantages as opposed to disadvantages induces the authors to claim that in children under the age of 6 years—when they, too, used to employ no anaesthesia—it is advantageous to perform bronchoscopic procedures under hibernation.

Application de l'hibernation artificielle dans les examens bronchoscopiques chez les nourrisons et les enfants.

Les auteurs rapportent les résultats de leurs observations concernant l'emploi de l'hibernation artificielle dans des examens bronchoscopiques effectués chez des nourrissons et des enfants âgés de 0 à 6 ans. Après avoir analysé quelque peu en détail les aspects favorables des effets pharmacologiques de l'hibernation, ils examinent les complications qui peuvent survenir. La mise en balance des avantages et des inconvénients de cette méthode amène les auteurs à conclure que l'application de l'hibernation leur paraît avantageuse pour les examens bronchoscopiques à pratiquer chez des sujets en dessous de 6 ans.

Die Anwendung der Hibernation bei der bronchoskopischen Untersuchung von Säuglingen und Kindern.

Ein Bericht über die Erfahrungen, die von der Anwendung der Hibernation für die bronchoskopische Untersuchung bei Säuglingen und Kindern im Alter von 0–6 Jahren gewonnen wurden, wird erstattet. Nach einer ausführlichen Analyse der günstigen Grundzüge im pharmakologischen Effekt der Hibernation werden die möglichen Komplikationen besprochen. Nach Abwägung der Vor- und Nachteile sind die Verfasser geneigt zu behaupten, dass es vorteilhaft ist, bei Kindern unter 6 Jahren Bronchoskopie im Zustand der Hibernation durchzuführen.

Uso de la hibernación en el examen broncoscópico de los lactantes y niños.

Se describe la experiencia obtenida con el uso de la hibernación en el examen broncoscópico de los lactantes y niños de 0 a 6 años de edad. Después de analizar con cierto detalle los aspectos propicios de los efectos farmacológicos de la hibernación, trátase de las complicaciones potenciales. Al estimar las ventajas e inconvenientes de la broncoscopia en condiciones de hibernación, los autores llegan a la conclusión de que es en efecto ventajosa en los pacientes de menos de 6 años de edad.

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Etudes spirographiques et oxymétriques chez le nourrisson

II. Influence de l'ingestion du repas liquide

par F. GEUBELLE

Chez l'adulte, les recherches concernant la mécanique respiratoire, ont permis de déterminer un ensemble de constantes physiologiques :

1° La mesure de la ventilation/minute au repos. Cette mesure est difficile : l'embout buccal et le pince-nez suppriment la respiration nasale; le masque comporte toujours un espace mort. Le sujet doit être au repos complet et apporter à l'épreuve une collaboration intelligente. L'étude du rapport entre la ventilation et la consommation d'oxygène permet d'apprécier la quantité d'oxygène utilisée par litre d'air ventilé : la diversité des valeurs considérées comme normales par différents auteurs (2, 9, 7, 11), confirme la difficulté d'obtenir une donnée précise.

2° La mesure de la capacité vitale et de ses composantes, la mesure de la ventilation maxima/minute, la mesure de la capacité pulmonaire utilisable à l'effort (épreuve de Tiffeneau) exigent également la collaboration du sujet.

3° La mesure de la ventilation au cours de différentes épreuves d'effort apporte d'utiles renseignements.

Le simple énoncé de ces différentes méthodes, permet de voir qu'il est très difficile et, le plus souvent, impossible de les appliquer au nourrisson. L'étude quantitative de la ventilation chez le nourrisson est réalisée depuis quelques années seulement (1, 3, 4, 5, 10, 13). Le volume respiratoire/minute, la fréquence, le volume circulant peuvent être mesurés d'une manière précise. La capacité vitale peut être appréciée dans une certaine mesure; le cri représente une inspiration maxima suivie d'une expiration forcée (15). Mais il n'existe pas encore, pour le nourrisson, d'épreuve fonctionnelle dans le sens qu'on accorde à ce mot chez l'adulte : imposer à l'individu certaines conditions, proches d'états physiologiques et mesurer sa ventilation, grâce à sa collaboration.

Puisqu'il est impossible d'obtenir une coopération de la part du nourrisson, on est obligé de l'observer dans les conditions normales de sa vie : sommeil, repos, ingestion du repas.

Parmi ces circonstances, l'ingestion du repas (prise du biberon) paraît réaliser un « effort » physiologique.

Une première série de mesures du pourcentage de saturation en oxygène (p.s.O.) faite à l'aide d'un oxymètre, nous a montré que chez 19 nourrissons sur 34, le p.s.O. est augmenté à la fin du repas et que, dans aucun cas, il n'est diminué. Au cours de ces mesures, nous avons pu voir d'importantes modifications de la fréquence, du rythme et de l'amplitude des mouvements respiratoires. Ces observations nous ont incité à : (1) mesurer d'une manière précise, la ventilation, et le p.s.O., simultanément chez le nourrisson normal au cours de l'ingestion d'un repas liquide; (2) voir dans quelle mesure cet acte de la vie quotidienne pouvait constituer une épreuve respiratoire.

Méthodes

a) La ventilation a été mesurée à l'aide de la méthode pléthysmographique décrite antérieurement (5).

b) Le pourcentage de saturation du sang cutané artérialisé a été mesuré à l'aide de la méthode oxymétrique exposée ailleurs (6).

c) Un enregistrement simultané des mouvements de succion et de déglutition a été réalisé à l'aide d'une méthode imaginée par Hytten (8), schématisée dans la figure n° 1. Elle consiste à raccorder une tétine à un styli-goutte d'une part, à un manomètre d'autre part. Ce tracé parallèle au tracé spirométrique permet de voir dans quelle mesure, les modifications de la ventilation peuvent être mises en relation avec l'ingestion du repas : chaque mouvement de succion et de déglutition est inscrit par la plume du manomètre.

Confortablement installé dans le pléthysmographe, l'enfant, sur le front duquel est ajusté et calibré l'oxymètre, reçoit un biberon. Si son appétit est normal et si l'orifice de la tétine est d'un calibre adéquat, ce repas est ingéré sans difficulté, en position couchée et sans interruption. Seuls sont considérés comme valables, les tracés où les mouvements de succion et de déglutition se succèdent sans arrêt.

A l'aide de ces trois techniques, nous avons : (*a*) mesuré et comparé la ventilation et l'oxygénation du nourrisson normal pendant le sommeil d'une part, à l'état de veille d'autre part; (*b*) mesuré et comparé la ventilation et l'oxygénation du nourrisson normal pendant le sommeil d'une part, pendant l'ingestion d'un repas liquide d'autre part.

Quatorze nourrissons, âgés de 4 à 20 semaines, convalescents d'infections bénignes (pharyngite, otite), ont été soumis à ces mesures. Les examens cliniques radiologiques et de laboratoire pratiqués auprès de ces enfants, étaient négatifs.

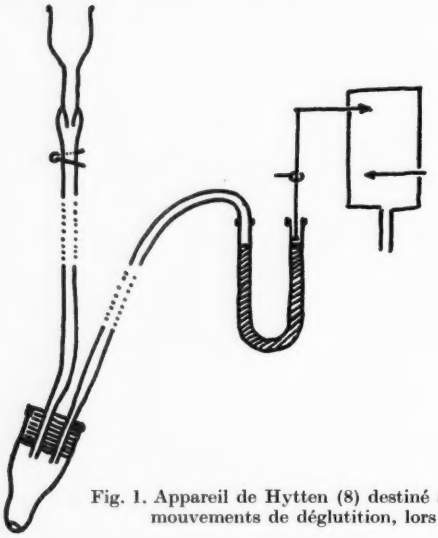

Fig. 1. Appareil de Hytten (8) destiné à enrégistrer les mouvements de déglutition, lors du repas.

Resultats

A. *Ventilation et oxygénation pendant le sommeil et à l'état de veille*

Le Tableau 1, indique : (*a*) le volume respiratoire/minute/kg de poids corporel observé lors du sommeil, (*b*) à l'état de veille, au repos, (*c*) la différence entre ces deux valeurs exprimées en % de la première, prise comme valeur de base, (*d*) le p.s.O. du sang cutané artérialisé lu à l'oxymètre, pendant le sommeil et l'état de veille.

TABLEAU 1

Ventilation et oxygénation du nourrisson normal au repos pendant le sommeil et à l'état de veille.

Enfant n°	Vol/min/kg (ml) Sommeil	Veille	Différence en %	p.s.O Sommeil % HbO_2	Veille % HbO_2
3	323	431	+33	93	93
5	217	226	+ 4	95	95
6	240	261	+ 8	95,5	95,5
7	251	315	+25	96	96
8	269	443	+64	96	96,5
9	334	594	+77	94	94,5
10	256	353	+37	95	95
12	288	390	+55	95	95,5
13	243	376	+54	94	95
14	317	260	+13	94	94

TABLEAU 2

Ventilation pendant le sommeil et lors de l'ingestion d'un repas liquide.

N°	Age (semaines)	Sommeil Vol/ min/ kg (ml)	Sommeil Fréqu./ minute	Sommeil Vol/ circ. (ml)	Biberon Vol/ min/ kg (ml	Biberon Fréqu./ minute	Biberon Vol. circul. (ml)	Différence en % Vol/ Vol/min/kg %
1	4	254	41	19,7	624	68	29,6	+ 145
3	4	323	40	26	551	70	26,7	+ 70
4	4	237	34	23,9	288	33	30,8	+ 21
6	5	240	28	30,3	381	52	29,8	+ 58
7	6	251	34	30,2	392	43	34,7	+ 56
8	8	269	40	27	451	60	30,5	+ 67
9	8	334	36	40,6	591	73	38,5	+ 76
10	8	256	38	28,9	355	45	34	+ 38
11	8	196	52	18,1	236	48	24,5	+ 20
12	18	288	40	38,5	532	68	42,3	+ 84
13	20	243	30	43,4	430	47	51,4	+ 77
14	20	317	40	36,5	422	70	27,5	+ 33

Les 10 nourrissons examinés montrent à l'état de veille une augmentation du volume respiratoire/minute/kg : elle oscille entre 4 et 77 % de la valeur de ce même volume mesuré lors du sommeil (moyenne : 35 %).

Cette augmentation du volume respiratoire est dûe à une augmentation simultanée de la fréquence et de l'amplitude des mouvements respiratoires dans 5 cas/10 à une augmentation de la fréquence et une diminution du volume circulant (tidal air) dans les 5 autres cas.

Le p.s.O. du sang cutané artérialisé, mesuré à l'oxymètre, à l'état de veille est identique à celui observé pendant le sommeil profond. Les variations du spot du galvanomètre correspondent à des modifications du p.s.O. de 0,5 à 1 % qui sont également observées pendant le sommeil.

B. *Ventilation et oxygénation pendant le sommeil et pendant l'ingestion d'un repas liquide*

Le Tableau 2, rassemble les valeurs : (*a*) du volume respiratoire/minute/kg, (*b*) de la fréquence respiratoire, (*c*) du volume circulant pendant le sommeil et lors de l'ingestion d'un repas liquide. Il s'agit de valeurs moyennes calculées sur un tracé d'une durée de 4 à 6 minutes. La colonne n° 9 indique, en % de la valeur du vol/min/kg pendant le sommeil prise comme base, la modification de ce volume lors de l'ingestion du repas. L'examen de ce tableau montre que :

a) chez les 12 nourrissons examinés, le volume respiratoire est augmenté. Cette augmentation est, en moyenne, égale à 62,3 % du volume respiratoire observé pendant le sommeil (valeurs extrêmes : + 20 % + 145 %).

b) le mécanisme qui explique cette augmentation est différente selon les cas :

fréquence respiratoire augmentée,			volume circulant		inchangé	chez	2	enfants
»	»	»	»	»	diminué	»	2	»
»	»	»	»	»	augmenté	»	6	»
»	»	inchangée	»	»	»	»	1	»
»	»	diminuée	»	»	»	»	1	»

c) chez trois enfants (N° 6–7 et 12), lors des 10–15 premières secondes d'ingestion du repas, les mouvements respiratoires sont peu fréquents et de faible amplitude : on note une période d'hypoventilation pendant laquelle l'enfant boit avidement et déglutit rapidement.

d) chez tous les enfants observés, le rythme respiratoire est très irrégulier. Les mouvements de déglutition sont intercalés ou superposés aux mouvements respiratoires.

e) pendant le repas, le p.s.O. lu à l'oxymètre varie :

1. *Au début du repas :* 3 enfants montrent une diminution de 1,2 et 4 % de leur p.s.O. (N° 6–7 et 12). Cette chute est de courte durée et correspond à la période d'hypoventilation signalée ci-dessus.
2. *Pendant le repas :* le p.s.O. reste stable chez certains enfants, augmente d'une manière régulière ou irrégulière chez d'autres.
3. *A la fin du repas :* 9 enfants sur 12, voient leur p.s.O. augmenté de 1,2 à 3 %; cette augmentation n'est pas en rapport avec l'âge. Ces 9 enfants montrent une augmentation du volume respiratoire lors du repas, mais comme l'indique le Tableau 3 : (*a*) tous les enfants dont la ventilation est augmentée, ne voient pas leur p.s.O. augmenté; (*b*) l'augmentation du p.s.O. n'est pas proportion-

TABLEAU 3

Ventilation et oxygénation pendant le sommeil et lors de l'ingestion d'un repas.

	Différence en % du vol/min/kg sommeil – repas	Modification du p.s.O. en fin de repas % Hb O_2
1	+ 145	+ 2,5
3	+ 70	+ 2
4	+ 20	+ 2
6	+ 58	+ 2,5
7	+ 56	0
8	+ 67	+ 1,2
9	+ 76	+ 3
10	+ 38	+ 3,5
11	+ 24	0
12	+ 84	– 2
13	+ 77	+ 1,2
14	+ 33	+ 1,2

nelle à celle de la ventilation. Chez un seul enfant (no. 12), le p.s.O. est diminué de 2 %; cette chute coïncide avec une augmentation importante du volume respiratoire.

Discussion

1. La ventilation augmente donc de 35 % en moyenne lorsque l'enfant passe du sommeil à l'état de veille, tout en restant calme et au repos. L'appréciation du calme chez un nourrisson est subjective et peut être difficilement objectivée; nous nous sommes efforcés de saisir les quelques rares minutes où le nourrisson est immobile, éveillé dans le pléthysmographe. Il est malaisé de réunir ces conditions auprès d'un nourrisson normal et il est pratiquement impossible d'obtenir « l'état basal » tel qu'il est compris chez l'adulte. La moindre excitation extérieure, la plus simple activité musculaire, entraîne aussitôt chez le nourrisson une respiration de fréquence et d'amplitude très variable. C'est pourquoi nous avons choisi, comme valeur de base, le volume respiratoire/minute/kg, mesuré pendant le sommeil et non la valeur mesurée à l'état de veille.

2. L'ingestion d'un repas liquide provoque une augmentation du vol resp./min/kg de 62 % en moyenne, par rapport aux valeurs mesurées pendant le sommeil. La prise d'un repas permet donc *d'induire* une hyperventilation à l'aide d'un mécanisme physiologique. Au cours de ces mesures, le débit de lait a été ajusté en fonction de l'appétit et des habitudes de l'enfant : par des mouvements de succion exercées sur la tétine, il peut règler la quantité de lait débitée par le styli-goutte mais il est possible de lui *imposer* un débit tel qu'une hyperventilation apparaît; elle peut être maintenue pendant plusieurs minutes.

3. L'observation clinique de nourrissons malades, présentant une affection respiratoire ou cardiaque congénitale, et ingérant un repas liquide, nous a montré que, pour certains d'entre eux, cet acte physiologique et l'hyperventilation qui l'accompagne, constituent une « épreuve ». Certains d'entre eux se cyanosent, d'autres ne modifient pas leur coloration. L'ingestion du repas, pourrait donc constituer une épreuve fonctionnelle, au sens habituel du mot.

4. L'hyperventilation seule, a été considérée comme une épreuve fonctionnelle et étudiée par Van Lingen & Whindborne (14). Des grands enfants et des adultes coopérants ont été invités à respirer rapidement et profondément pendant une minute, en position assise. Leur p.s.O. mesuré à l'aide d'un oxymètre type Millikan (12) augmente de 2 à 7 % (moyenne : 3,5 %) d'Hb O_2. Différents mécanismes physiologiques, peuvent expliquer cette modification du p.s.O. : brassage plus important des gazs alvéolaires, aération meilleure de régions du parenchyme pulmonaire mal ventilées, modifications circulatoires.

5. L'hyperventilation induite par le biberon et l'hyperventilation volontaire, étudiée par Van Lingen, ne sont pas strictement comparables : en effet, si au cours du repas, l'activité de l'enfant est minimale, il faut cependant tenir compte des efforts musculaires requis par la succion et l'hyperpnée elle-même. Seule, une mesure simultanée de la consommation d'oxygène et du p.s.O. peut nous indiquer d'une manière plus précise l'importance de cet effort musculaire.

6. Dans un seul cas (N° 12) on note à côté d'une augmentation importante de la ventilation, une chute de p.s.O. de 2 %. L'examen du dossier clinique montre que ce nourrisson a présenté une pharyngite et une bronchite; la température a oscillé entre 37°5 et 38°C. pendant 7 jours. Les mesures de ventilation ont été faites 10 jours après; les examens cliniques, radiologiques et de laboratoire, ne montraient plus rien de particulier. Il est le seul nourrisson à présenter une diminution du p.s.O. lors du repas. Nous l'avons inclus dans la série des enfants normaux, parce qu'aucun fait pathologique *clinique* ne peut être relevé : mais il est possible que cette réaction anormale au cours de l'épreuve traduise la présence d'une séquelle *fonctionnelle*, si minime soit-elle, de cette bronchite.

Conclusions

La mesure simultanée de la ventilation et de l'oxygénation chez le nourrisson normal montre que :

1° la ventilation augmente de 35 % en moyenne lorsque l'enfant passe du sommeil à l'état de veille; de 62 %, par rapport à la valeur mesurée pendant le sommeil lorsqu'il ingère un repas liquide.

2° que l'hyperventilation au cours du repas liquide, coincide dans la grande majorité des cas, avec une augmentation du p.s.O. de 1,2 à 3,5 % d'HbO_2.

3° que cette hyperventilation, induite par l'opérateur et cependant physiologique, pourrait constituer une épreuve fonctionnelle. Nous pensons qu'une étude ultérieure permettra d'en préciser la nature exacte.

Spirographic and oxymetric findings in infants. II. The influence of ingestion of a liquid meal.

Simultaneous determination of ventilation and oxygenation in infants showed that (1) ventilation shows an average increase of 35 % as the infant passes from sleep to a waking condition, and an increase of 62 % of the value determined during sleep when a liquid meal is ingested; (2) hyperventilation during ingestion of a liquid meal coincides in the majority of cases with an increase in the percentage of oxygen saturation from 1.2 to 3.5 % HbO_2; (3) this hyperventilation, induced by the observer and yet physiological, may constitute a function test, the exact nature of which awaits further investigation.

Spirographische und oxymetrische Studien beim Säugling. II. Der Einfluss der Einführung einer flüssigen Mahl.

Die gleichzeitige Messung der Ventilation und der Sauerstoffsättigung beim normalen Säugling zeigt, dass 1) die Ventilation durchschnittlich um 35 % ansteigt, wenn das Kind aus dem Schlaf in den Wachzustand übergeht und um 62 % über den im Schlaf gemessenen Wert, wenn es ein flüssiges Mahl einnimmt 2) die Hyperventilation während der Einführung des flüssigen Mahles im grössten Teil der Fälle mit einer Steigerung der prozentuellen Sauerstoffsättigung einhergeht, nämlich 1,2 bis 3,5 % HbO_2; 3) diese vom Operateur verursachte, jedoch physiologische Hyperventilation eine Funktionsprüfung darstellen könnte. Der Verfasser nimmt an, dass sich durch weitere Studien die genaue Natur dieser Steigerung feststellen lassen wird.

Estudios espirográficos y oximétricos en los lactantes. II. Influencia de la ingestión de dieta líquida.

La medición simultánea de la ventilación y de la oxigenación en el lactante normal, indica que: 1. La ventilación aumenta en promedio con un 35 % cuando el niño pasa del sueño al estado de vigilia, y con un 62 % respecto al valor medido durante el sueño, cuando ingiere una comida líquida. 2. La hiperventilación en el curso de la comida líquida, coincide, en la gran mayoría de los casos, con un aumento del porcentaje de la saturación con oxígeno, del 1, 2 al 3, 5 % de HbO_2. 3. Esta hiperventilación, inducida por el operador, y no obstante fisiológica, pudiera constituir una prueba funcional. Opinamos que un estudio ulterior permitirá precisar su naturaleza exacta.

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Sporadic Congenital Spherocytosis Associated with Congenital Hypoplastic Thrombocytopenia and Malformations

by ROLF ZETTERSTRÖM and BENGT STRINDBERG

The purpose of this report is to describe the clinical findings in two non-related children with a syndrome characterized by severe malformations, thrombocytopenia due to hypoplasia of the megacaryocytes and a hemolytic disease which according to its characteristics might be considered to be caused by a congenital intracorpuscular red cell defect. The relation of this syndrome to other similar clinical conditions such as the Fanconi type anemia and congenital hypoplastic thrombocytopenia associated with malformations (10–14) will be discussed.

Case Reports

CASE 1.

A. L., a girl, was admitted to the Pediatric Clinic, Karolinska Sjukhuset, one day after birth because of a hemorrhagic disease and deformity of the forearms.

She was the second child of healthy parents. The family history was irrelevant and no consanguinity existed between the parents. The child was born at term; the birthweight was 3620 g. Pregnancy and delivery were uncomplicated. The infant was born with a deformity of both arms, due to the absence of both radii, resulting in diminutive forearms with abducted hands. The child otherwise appeared healthy at birth. When born, she received 5 mg of synkavite. One day after birth melena and hematemesis occurred.

On admission, 28 hours after birth, the infant was found to be in a relatively good condition, she had a violent cry and there were no symptoms of respiratory distress. There was no pallor and the infant was not jaundiced. She was slightly edematous. Small amounts of fresh blood were passed from the bowel. Numerous scattered petechiæ were found on the lower part of the trunk and on the legs. There was no gross subcutaneous bleedings nor were there any subserous bleedings in the oral cavity. No lymphadenopathy was observed. She had a moderate abdominal distension and the liver was slightly enlarged and was palpable 2.5 cm below the costal margin. There was a marked splenomegaly; the spleen reached almost to the umbilicus. No other abnormality was found on physical examination.

Laboratory investigations.—The hemoglobin level was 14.9 g per 100 ml. There were 50,000 white cells per c.mm with a preponderance of granular cells and a marked

shift to the left. The number of nucleated red cells was 5000 per c.mm. Platelet count 30,000 per c.mm. The bleeding-time was in excess of 25 minutes and the clotting time was slightly prolonged (18 minutes and 25 seconds). Prothrombin time was within normal limits. There was a positive tourniquet test. Her blood group was $A_2Rh(+)$, and the direct, as well as the indirect, Coombs' tests were negative. Investigation of tibial marrow on two occasions during the first week after admission showed a very active leucopoiesis and a normoblastic erythropoiesis of normal intensity. However, prolonged search on several films from each specimen failed to show any mature or early forms of megacaryocytes. No cytomegalic inclusion bodies were found in repeated urinary sediments. Chromatographic investigation of urinary amino acids (according to the method of Dent (1)) did not reveal any abnormalities. Hematologic investigation of the parents showed quite normal values. The mother had a normal platelet count and a serologic investigation failed to reveal signs of isoimmunization. The Wasserman reaction was negative in the mother and the child, and there was no serologic evidence of toxoplasmosis.

Course of the disease.—The child was under control up to an age of almost one year. After admission a tentative diagnosis of congenital hypoplastic thrombocytopenia associated with a skeletal malformation was made. This diagnosis was based on the absence of megacaryocytes in the bone marrow.

The main hematologic data and some of the clinical symptoms and findings during the period of observation are shown in Fig. 1. As is illustrated from this figure, relatively massive hemorrhagic symptoms were present during the first month of life. For 10 days the stools continued to be bloodstained. At the same time hematemesis occasionally occurred, and there were repeated outbreaks of abundant petechiae. After this period there was an improvement with fading of petechiae and changing of the stools from melenic to normal. Within another week the severe hemorrhagic symptoms returned. This relapse, which persisted for one week, was followed by occasionally appearing petechiae as the only manifestation of the hemorrhagic disorder. The spleen, which was highly enlarged in the neonatal period, subsequently decreased in size.

Despite the marked clinical improvement after the first month of life, the number of circulating platelets remained very low for another 5 months. The count varied between 13,000 and 45,000 per c.mm. The marked prolongation of the bleeding-time and the reduction of the capillary resistance also persisted. During the second half-year of life, however, a significant rise of the platelet count up to 75,000–100,000 per c.mm occurred. At that time also, a few platelet precursors were found in sternal marrow smears. Furthermore, some control of the bleeding tendency appeared as shown by a decrease of the bleeding-time and some improvement of the capillary fragility test.

On admission, a relatively mild anemia was present. Subsequently, however, there was a marked progression and at an age of one month the hemoglobin level was only 5.8 g per 100 ml. During the first period of observation, this anemia, which was normochromic and associated with an intense reticulocytosis, was interpreted as the result of the melena and hematemesis. Since, however, the low hemoglobin level as well as signs of an intense erythropoiesis persisted, even after the blood losses subsided, another etiology had to be considered. Examinations of blood films showed a marked microspherocytosis with about 5–10 per cent abnormal red cells. The mean red cell diameter was also found to be rather low. Thus, there were many indications of a hemolytic anemia, although the serum bilirubin level was found to be normal. As will

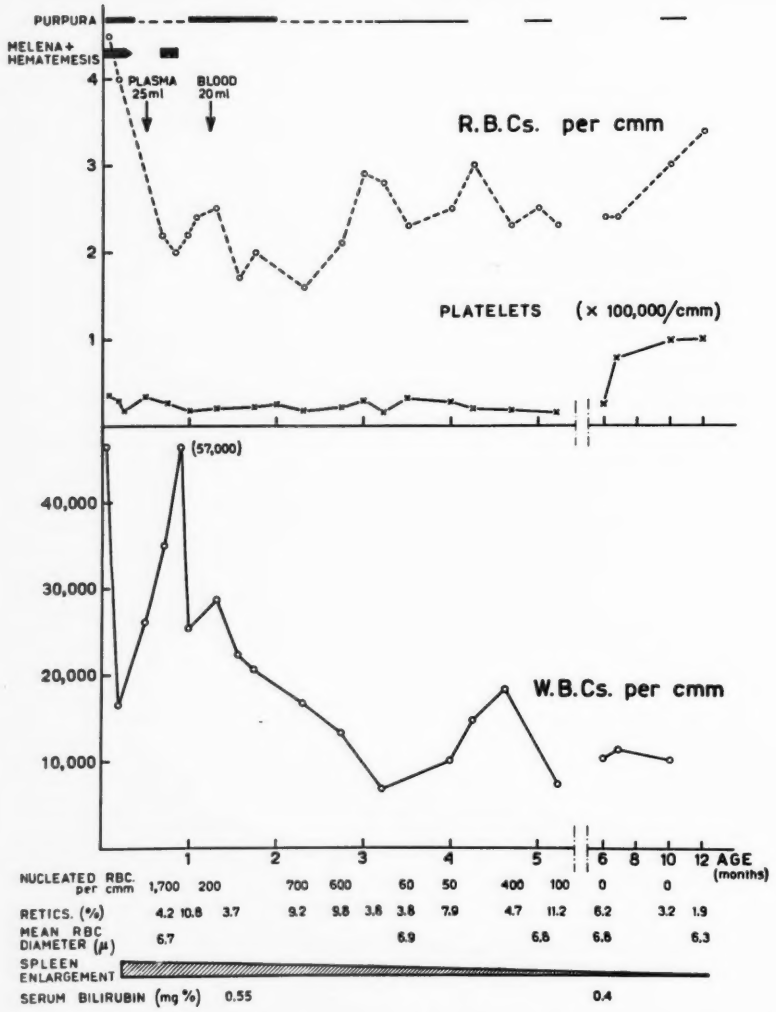
PURPURA
MELENA + HEMATEMESIS
PLASMA 25ml
BLOOD 20ml
R.B.Cs. per cmm
PLATELETS (× 100,000/cmm)
(57,000)
W.B.Cs. per cmm
AGE (months)
NUCLEATED RBC. per cmm 1,700 200 700 600 60 50 400 100 0 0
RETICS. (%) 4.2 10.8 3.7 9.2 9.8 3.8 3.8 7.9 4.7 11.2 6.2 3.2 1.9
MEAN RBC DIAMETER (μ) 6.7 6.9 6.8 6.8 6.3
SPLEEN ENLARGEMENT
SERUM BILIRUBIN (mg %) 0.55 0.4

Fig. 1. Main hematologic data during the course of the disease in Case 1. At birth she was found to present deformity of the forearms due to absence of radii bilaterally. Hemorrhagic symptoms appeared about 24 hours after birth.

be reported later, further investigations confirmed this diagnosis, the hemolytic disease most likely being due to an intracorpuscular defect.

The white cell count which was very high on admission remained elevated for the first month of life. Following admission, the count was usually within the normal

Fig. 2. Photograph of Case 1 at an age of 11 months showing the deformity of the forearms.

range. There were no abnormalities in the leucopoiesis as revealed from bone marrow smears and, except for the marked shift to the left during the period of leucocytosis, the differential count was normal.

In spite of the anemia, the general condition of the child remained good, with satisfactory somatic and mental development. The appearance of the child at an age of 11 months is illustrated in Fig. 2. Because of the arm deformities, orthopedic treatment was started at an age of 10 months; no specific therapy was otherwise given.

Summary of the clinical features of Case 1.—In a newborn girl, with a congenital deformity of the forearms due to complete absence of both radii, symptoms of a hemorrhagic disease which was found to be due to hypoplastic thrombocytopenia appeared within the first day of life. The infant was under observation for 12 months. During the first 6 months of life, there was a marked thrombocytopenia. Later a slight but significant rise of the platelet count took place. In spite of the subsidence of the blood loss at the age of one month, an anemia persisted. According to the hematologic investigation this anemia was most likely due to a hemolytic disease associated with some red cell intracorpuscular defect. Leucopoietic activity was completely intact.

CASE 2.

Å. D., was a female admitted to the Pediatric Clinic, Karolinska Sjukhuset, at an age of 7 months because of congenital thrombocytopenia, recurrent urinary tract infections and congenital heart disease.

She was the only child of rather old but healthy parents. No consanguinity existed between the parents and no hematologic disorders were known in the family. Pregnancy and delivery were uneventful. The girl was born at term and her birthweight was 3810 g. She had 2 teeth at birth. During the days following birth there was a slight generalized cyanosis but she had no symptoms of respiratory distress. In the neonatal period abundant petechiae appeared but no other symptoms of a hemorrhagic disorder were present. The petechiae were considered to be due to a thrombocytopenia, as the platelet count was found to vary between 40,000 and 100,000 per c.mm. When the infant was 2 months old a systolic murmur was heard over the heart and a diagnosis of congenital heart disease was made. Because of cyanosis the baby was admitted to a community hospital at an age of 4 months. On examination it was found that the infant still had petechiae and that the thrombocytopenia persisted. Otherwise the hematologic investigation did not reveal any abnormalities. She also had a urinary tract infection which was treated with antibiotics. Since this infection recurred frequently a urinary tract malformation was suspected and the girl was admitted to this clinic for further work-up.

On admission, the physical examination revealed a slightly underdeveloped 7-month-old girl with a weight of 6300 g. She was moderately dyspnoeic. On crying, a mild cyanosis developed in her face, otherwise the colour of the skin was normal. No petechiae or other symptoms of a hemorrhagic disorder were present. A systolic murmur was heard over the heart. The liver was felt just below the costal margin and there was a mild splenomegaly.

Laboratory investigations.—During the 3 weeks she stayed in the hospital, the hemoglobin level varied between 11.5 and 13.8 g per 100 ml. The number of red cells was 4.1–4.8 millions per c.mm. She had approximately about 300 nucleated red cells per c.mm and there were 1.4–7.0 per cent reticulocytes. On the first examination, she had a marked leucocytosis with 20,000 white cells per c.mm, 60 per cent of which were leucocytes. Within 2 weeks, the leucocytosis disappeared and the white cell count dropped to 5800 per c.mm. There was a constant thrombocytopenia, with the values varying between 62,000 and 105,000 per c.mm. Investigation of the tibial marrow showed a rather active normoblastic erythropoiesis, a normal leucopoiesis, and some megacaryocytes of normal appearance. Hematologic investigation of the mother did not reveal any abnormalities. The Wasserman reaction was negative in the mother and the child.

She had proteinuria and a massive pyuria as symptoms of a urinary tract infection, which after treatment with antibiotics, disappeared. No cytomegalic inclusion bodies were found in the urinary sediment. There was a normal excretion of amino acids in the urine. Roentgenological investigation of the urinary tract showed a hydronephrosis on the right side probably due to an uretero-pelvic obstruction. The parenchyma of the right kidney was markedly reduced and the excretory capacity was very low. On the left side, the renal pelvis was slightly dilated and some intrapapillary calcifications were visualized.

X-ray investigation of the chest organs showed a rotation of the heart and a right ventricular hypertrophy. The lower part of the left lung was atelectatic and there were

Fig. 3. Shows Case 2 at an age of 18 months. At that time there was a slight physical as well as mental retardation.

TABLE 1

Case 2. Main hematologic data during the period of observation.

With regard to her cardiac disease the hemoglobin level was rather low.

Age (months)	Hb (g %)	Red cells × 1000,000	Reticulocytes (‰)	Thrombocytes × 1000	White cells × 1000	Nucleated red cells per mm³	Serum bilirubin (mg%)	Mean diam. of red cells (μ)
7	13.8	4.9	14	105	19.9		0	
7.5	11.5	4.1	37	64	6.1	300		6.7
9.5	12.1	5.6	34	60	4	200		6.2
10	11.0	4.0	51	56	4.8			
15.5	14.4	5.8	23	128	7.1			6.6

signs of increased blood flow in the lungs. The electrocardiogram showed evidence of right ventricular hypertrophy.

Course and treatment.—The child has been under control up to an age of 19 months. There was a slight physical, as well as mental retardation. At an age of 18 months her weight was 8900 g. At this age she was not able to walk without support. The cyanosis showed a tendency to increase. Occasionally petechiae appeared but there were no other hemorrhagic symptoms. Fig. 3 is a picture of the girl when she was 18 months old.

The main hematologic data during the follow-up are given in Table 1. As is shown from this table the moderate thrombocytopenia persisted. Since hemoglobin level remained relatively low in spite of an occasionally rather high reticulocyte count and the presence of a severe cyanotic heart disease, a hemolytic disease was suspected. A large number of spherocytes were also found in blood smears. The number of white cells as well as the differential count remained normal. The bleeding time was normal or only slightly prolonged. Clotting time, prothrombin consumption, thromboplastin generation tests, and clot retraction were all normal. There was a constant reduction of the capillary resistance as demonstrated from the Rumpel-Leede test. The serum bilirubin level was not elevated.

At an age of 10 months a uretero-pelvic resection was performed on the right side because of the marked hydronephrosis. After this operation there was no further increase of the dilatation of the pelvis as revealed from roentgenological examinations.

At an age of 19 months a catheterization and angiocardiographic investigation of the heart was performed. The catheter was found to pass from the pulmonary artery out into the aorta. The pressure was very high both in the right ventricle and in the pulmonary artery and the values for the oxygen saturation were in accordance with the concept of a right to left shunt. Contrast injected into the right ventricle passed from the pulmonary artery out into the descending aorta. No communication between the ascending and descending part of the aorta was visualized. The final cardiologic diagnosis was aortic coarctation of infantile type with fetal circulation. Surgical treatment was considered to be contra-indicated because of the presence of a high pulmonary resistance.

Summary of Case 2.—In a newborn girl, with multiple severe malformations (congenital heart disease and hydronephrosis), a congenital thrombocytopenia was diagnosed. This thrombocytopenia which persisted during the 19 months when the child was under control was rather moderate and petechiae were the only symptoms of a hemorrhagic disorder. Although some platelet precursors were found in bone marrow smears, the thrombocytopenia was considered to be of the hypoplastic group because the clinical features did not fit in with a diagnosis of a megacaryocytic type. With regard to the severe cyanotic congenital heart disease, the hemoglobin level was rather low. Since the reticulocyte count was elevated almost regularly and because of the presence of spherocytes, a tentative diagnosis of a hemolytic disease was made.

Investigations with Regard to the Presence of Hemolytic Disease

Since in both patients the routine examination revealed such features that a hemolytic disorder was suspected, a more detailed hematologic investigation was performed.

Methods.—The electrophoretic mobility of the hemoglobin was investigated as described by Block, Durrum & Zweig (2). Determination of the resistance to alkali denaturation was carried out according to Singer, Chernoff & Singer (3). Osmotic

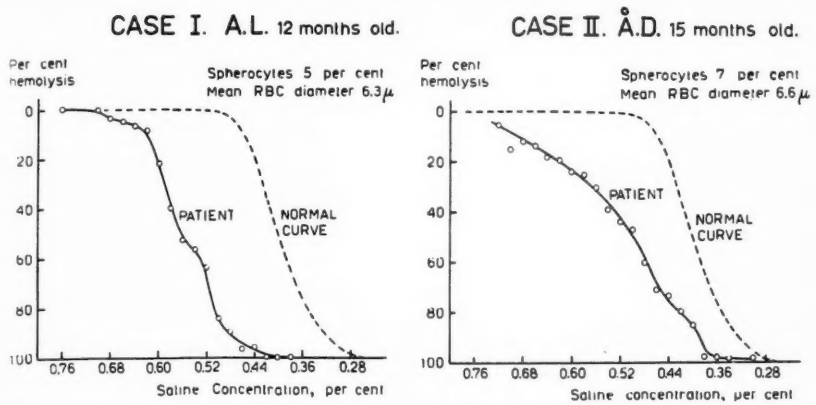

Fig. 4 (*left*). Case 1. Osmotic fragility of red cells. The low resistance to hypotonic saline as well as the asymmetry of the curve is illustrated.

Fig. 5 (*right*). Case 2. Osmotic fragility of red cells. The curve has about the same shape as in Case 1.

fragility was determined in the conventional way without any previous incubation. The survival of the patients' own red cells and of transfused normal red cells was investigated with the aid of the labeled chromium method as described by Gray and Sterling (4).

Results.—Paper electrophoresis of hemoglobin samples from both patients revealed the same migration as hemoglobin from normal individuals at pH 8.6. At an age of 11 and 18 months, respectively, less than 2 per cent of the total hemoglobin had the same resistance to alkali as fetal hemoglobin.

The results of the osmotic fragility tests are shown in Figs. 4 and 5. As is clearly demonstrated there was, in both patients, a marked reduction of the resistance to hypotonic saline which is in accordance with the observation that there were a large number of spheroidal red cells in the peripheral blood. The distribution curves of the osmotic fragility were asymmetrical and biphasic, a fact which has been explained as being due to the absence of a large proportion of the cells showing hemolysis at tonicity levels above 0.5 per cent saline, probably caused by a removal within the spleen (5).

As is shown in Fig. 6, there was in Case 1 a marked reduction of the survival of the patient's own red cells, the half life time being 30–40 days. In Case 2 the mean survival time was calculated to be the same. The fact that normal red cells transfused to the patients were found to have a normal life span of about 120 days might indicate that the hemolytic disorder is caused by an intracorpuscular defect (6–7).

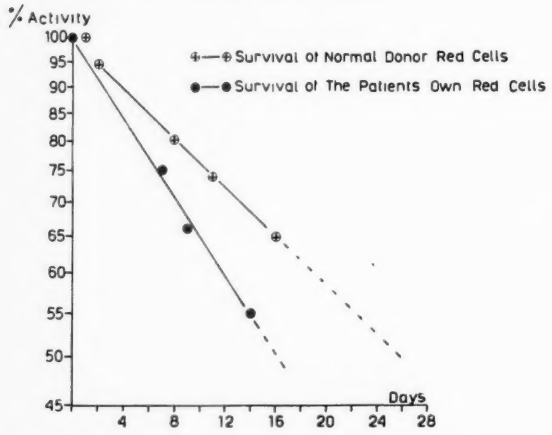

Fig. 6. Case 1. Survival of the patient's own red cells and of normal donor cells as determined with the labeled chromium method.

There was a marked reduction of the survival time of the patient's own cells (half-life 30–40 days) whereas normal donor cells had a normal survival.

Discussion

The two patients reported exhibited a syndrome characterized by congenital malformations, thrombocytopenia, and a hemolytic disease. In Case 1 there was a deformity of the forearm due to the absence of the radii. Case 2 had bilateral hydronephroses and a severe congenital heart disease. In both children the thrombocytopenia, which was marked during the first months of life but then successively improved, was most likely caused by a hypoplasia of the megacaryocytes, i.e. by a partial bone marrow failure. The mild hemolytic disease diagnosed in both patients exhibited the classic feature of hereditary spherocytosis although there was no evidence of inheritance.

Some of the clinical features of the patients described in this report resemble those found in the Fanconi type anemia (8), a genetically determined clinical entity characterized by pancytopenia due to chronic bone marrow failure and by the presence of multiple congenital anomalies. (For references cf. a recent review on this subject by Dawson (9).) There are, however, many differences as to the consideration of cases presented here. In the Fanconi syndrome, there is usually a macrocytosis and there is no evidence suggesting a hemolytic disease. Furthermore, in our patients the hypoplasia of the megacaryocytes was the only sign of bone marrow failure, the erythropoietic as well as the myelopoietic activity being normal.

A few cases of congenital hypoplastic thrombocytopenia, i.e. thrombocytopenia due to a congenital absence or a marked reduction in the megacaryocytes, without any reduction in the other elements of the bone marrow, have been described (10–14). In most instances of this disorder hemorrhagic symptoms were present at or shortly after birth.

Of 5 cases with this syndrome which have been previously reported, only one was alive at an age of one year (12). The others had expired, most probably from their hemorrhagic disease. In the single infant without fatal outcome during infancy, the hemorrhagic symptoms subsided due to a rise of the platelet count. In this infant splenectomy had been performed.

Many of the features in our two patients are common to those in the well limited group of congenital amegacaryocytic thrombocytopenia. The types of malformations which are present in our cases have also been reported previously in this syndrome. In two instances there was absence of radii bilaterally (12, 14); in one a severe cardiac malformation was found at autopsy (10); and in another one there was a renal anomaly (11). Hemolytic disease has never been diagnosed in connection with this syndrome. However, one of the cases which was reported (14) had a low hemoglobin level associated with the presence of normoblasts in the peripheral blood; despite the absence of blood loss, findings were present which raised the possibility of a hemolytic anemia. Thus, the possibility cannot be excluded that our cases belong to this congenital thrombocytopenia syndrome. Although not diagnosed, a more or less mild hemolytic disease might have been present.

Whether the syndrome which is present in the two patients reported in this article developed as the result of a genetic defect or as the sequel of an injury to the fetus cannot be deduced. Neither in our patients, nor in those which earlier have been diagnosed as congenital hypoplastic thrombocytopenia, has there been any indications of inheritance which is in contrast to the Fanconi type anemia, a disease which seems to be due to a recessive gene (15).

The concurrent occurrence of thrombocytopenia, and such a malformation as the absence of both radii, has been attributed to a fetal injury (14). This theory is based upon the fact that platelet production is known to begin at the same stage in embryogenesis as that in which this type of defect might arise, i.e. during the second gestational month (16). It is more difficult to reconcile in what way some agent with a teratogenic action or another type of injury can give rise to such a hematologic disorder as a congenital spherocytosis, a disease which is most likely caused by an error of erythrocyte metabolism (17), i.e. by some enzymatic defect. However, the possibility remains that the same injury which might have caused the

partial bone marrow failure, as well as the congenital malformations, might also have induced a chronic metabolic defect of the erythrocytes due to some damage to the genes in the developing erythropoietic tissue.

Summary

Two cases of congenital hypoplastic thrombocytopenia associated with a hemolytic disease and congenital malformations are described. In one of the children, there was a deformity of the forearms due to absence of both radii; and in the other, there was a severe cardiac malformation and hydronephroses.

Studies of the hemolytic disease in both cases revealed features typical of congenital spherocytosis although there were no indications of inheritance.

The relation of this syndrome to other similar clinical conditions and its possible pathogenesis is discussed.

Microsphérocytose congénitale sporadique associée à une thrombocytopénie hypoplastique et à des malformations congénitales.

Les auteurs donnent la description de deux cas de thrombocytopénie congénitale accompagnée d'ictère hémolytique et de malformations congénitales. Un de ces enfants présentait une malformation des avant-bras dont les deux radius étaient absents; le second était atteint d'une malformation cardiaque sévère et d'hydronéphrose. L'examen de l'ictère hémolytique a fait apparaître dans les deux cas des signes de microsphérocytose congénitale; on n'a cependant découvert aucun indice qui permette de dire qu'il s'agissait là d'affections héréditaires. Les auteurs examinent ensuite les relations qui peuvent exister entre ce syndrome et d'autres états cliniques analogues, puis ils étudient les hypothèses que l'on peut faire en ce qui concerne sa pathogénèse.

Sporadisch auftretende angeborene Sphärocytose verbunden mit angeborener hypoplastischen Thrombocytopenie und Missbildungen.

Es werden zwei Fälle von angeborener hypoplastischen Thrombocytopenie in Verbindung mit hämolytischer Krankheit und kongenitalen Missbildungen beschrieben. Bei einem der Kinder bestand eine Missbildung der Vorderarme, bedingt durch die Abwesenheit beider Radii, beim anderen eine schwere Herzmissbildung und Hydronephrose. Untersuchungen der Natur der hämolytischen Krankheit in beiden Fällen ergaben typische Befunde für angeborene Sphärocytose, wenn auch ohne Anzeichen von Erblichkeit. Das Verhältnis dieser Syndrome zu anderen ähnlichen klinischen Zuständen und die mögliche Pathogenese werden erörtert.

Esferocitosis congénita esporádica asociada con trombocitopenia hipoplástica congénita y malformaciones.

Descripción de dos casos de trombocitopenia hipoplástica congénita asociada con una enfermedad hemolítica y malformaciones congénitas. Uno de los niños presentaba una deformidad en ambos antebrazos, debida a la ausencia del hueso radio; el otro niño presentaba una malformación cardíaca grave e hidronefrosis. El estudio de la enfermedad hemolítica en ambos casos reveló aspectos típicos de esferocitosis congénita, aunque no hubieran indicaciones hereditarias. Discusión de la relación este síndrome con otras condiciones clínicas similares y probable patogénesis.

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Untersuchungen über einen Hauttest durch Scarification mit Cantharidin bei Kindern mit akutem Gelenkrheumatismus

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Zweck dieser Arbeit ist die vergleichende Analyse des Inhalts von Cantharidinblasen und des Blutserums bei Kindern, die an Gelenkrheumatismus leiden. Zugleich soll die Permeabilität des Bindegewebes während verschiedener Krankheitsphasen untersucht werden.

Angeregt wurden wir durch die Erfahrung, dass bei akutem Gelenkrheumatismus die durch den Streptococcus erzeugte Hyaluronidase zu einem Abbau der Hyaluronsäure und damit zu einer erhöhten Bindegewebspermeabilität führt. Wie aus der Literatur hervorgeht, haben sich auch andere Autoren mit den Beziehungen zwischen Bindegewebspermeabilität und Hyaluronidase befasst, ohne dabei zu einheitlichen Ergebnissen zu kommen.

1. Nach Bywaters, Holborow & Keech dauert die Erhöhung der lokalen Gewebspermeabilität der Haut nach Hyaluronidaseinjektion bei unbehandelten Rheumatikern länger als bei den mit Aspirin oder Cortison oder ACTH behandelten Patienten.

2. Glassman, Blumenthal, Beckfield & Seifter haben den Einfluss von Hyaluronidase auf die Permeabilität der Kapillaren studiert und dabei eine beschleunigte Rückbildung einer durch Hautreizmittel (wasserlösliche oder öllösliche) hervorgerufenen Entzündung gefunden.

3. Ansell, Antonini & Glynn fanden, dass Cantharidinblasen bei rheumatischen Kindern einen kleineren Durchmesser zeigen als bei gesunden. Diese Beobachtung wird durch erhöhte lokale Gewebsdurchlässigkeit erklärt. Während der Behandlung mit ACTH sah man noch kleinere Durchmesser der Cantharidinblasen. Man führt dies auf die durch ACTH veränderte Capillarpermeabilität zurück.

4. Creysel & Matrey verglichen die Ergebnisse von chromatographischen Untersuchungen der Aminosäuren des Inhaltes von Cantharidinblasen mit solchen des Blutserums bei nicht näher angeführten Erkrankungen. Typische Unterschiede fanden sich dabei nicht.

Eigene Untersuchungen

Bei 47 Kindern im Alter von 4–14 Jahren haben wir den Inhalt von Cantharidinblasen im Vergleich zum Blutserum untersucht. 38 Patienten

waren wegen akuten Gelenkrheumas behandelt. Die übrigen 9 waren gesund. Zur Behandlung dienten Cortison und Aspirin. Einigen Patienten wurde Aspirin allein gegeben.

Technisches

1. *Gewinnung des Untersuchungsmaterials.* Nach lokaler Alkoholreinigung wird eine Hautfläche von 5 × 5 mm am Bauch für 16 Stunden mit dem Cantharidin belegt. Man beobachtet das Entstehen einer Blase von wechselnder Art (Grösse, umgebender Hof usw.). Der Inhalt wird abpunktiert und die verbliebene Läsion mit Sulfonamidpuder bestreut. Binnen einer Woche tritt völlige Heilung ein. Wir fanden diese Methode schmerzlos und frei von nennenswerten Komplikationen.

2. *Biochemische Untersuchungen der Blasenflüssigkeit im Vergleich zum Blutserum.* Die Farbe der Blasenflüssigkeit schwankte zwischen hell- und dunkelgelb; 15–30 Min. nach der Entnahme kam es zu einer Trübung. Die Menge betrug jeweils etwa 3–5 ml. Es wurden bestimmt:

a) *Ionogramm.* Kalium, Natrium (Flammenphotometrie EEL), Calcium (nach Kramer & Tisdal, modifiziert nach Clark & Collip), Phosphor (nach Fiske & Subbarow), Chlor (nach Ruszuyak).

b) *Gesamteiweiss* (nach Greenberg/Photometer Leitz).

c) *Die qualitative Untersuchung der Eiweisskörper* wurde mit Elektrophorese durchgeführt. (Papierelektrophorese Elphor H nach Bender & Hobein. Puffer: Diäthylbarbiturnatrium nach Michaelis, pH 8,6).

d) *Aminosäuren.* Für die Bestimmung der Aminosäuren in der Blasenflüssigkeit bzw. im Blutserum wurde die zweidimensionale Methode der Papierchromatographie verwendet. 0,05 ml. Blasenflüssigkeit bzw. Blutserum wurden auf Whatmann No. III aufgebracht. Als erstes Lösungsmittel wurde wasserhaltiges Phenol und als zweites Pyridin–Amylalkohol–Wasser verwendet. Zum Phenol wurde Ammonium und Cyannatrium und zum Pyridin, Diäthylanin zugesetzt. Es wurde mit 0,1 %igen Ninhydrinlösung in wassergesättigtem Butanol besprüht, bis die Flecken hervortraten. Nach 24stündiger Lagerung bei Zimmerwärme wurden die Flecken abgelesen. Die Flecken sind charakterisiert durch ihre Farbintensität. Diese wurden mit den Flecken einer Standart-Taurinlösung verglichen.

3. *Mikroskopische Untersuchung der Blasenflüssigkeit.* Es fanden sich segmentkernige Leukozyten. Keine Mikroorganismen.

Ergebnisse

Unsere Fälle haben wir in vier Gruppen eingeteilt.

Gruppe A (9 gesunde Kinder)

a) *Ionogramm:* Die Resultate der Untersuchung des Ionogramms der Blasenflüssigkeit bzw. des Blutserums waren folgende:

	Blutserum mg %	Blasenflüssigkeit mg %
Ca	10–12	10,5–12
K	16–21	16,0–22
Na	325–360	320–350
P	4–6	4–6
Cl	525–600	525–580

b) *Gesamteiweiss:* Das Gesamteiweiss der Blasenflüssigkeit schwankte zwischen 3,50 g % und 6,15 g %, das Gesamteiweiss des Blutserums schwankte zwischen 5,80 und 7,70 g %. Aus der Differenz der Durchschnittswerte des Blutserums (6,69 g %) und der Blasenflüssigkeit (4,84 g %) ergab sich ein Unterschied von 1,85 g %.

c) *Elektrophorese:* Kein wesentlicher Unterschied im Elektrophoresebild der Blasenflüssigkeit bzw. des Blutserums.

d) *Aminosäuren:* Das Blutserum und die Blasenflüssigkeit enthielten quantitativ und qualitativ die gleichen Aminosäuren (8–11) d.h. Alanin, Glykokol, Valin, Glutaminsäure, Glutamin, Thyrosin, Threonin, Cystinsäure, Arginin, Lysin, Leucin. Ihre Fleckenintensität schwankte zwischen 10–30 γ Taurin.

Gruppe B

Diese Gruppe setzte sich aus 14 Kindern zusammen, die an akutem Rheumatismus litten. Die Untersuchungen wurden in der akuten Krankheitsphase und vor dem Beginn der Behandlung durchgeführt.

a) *Ionogramm:* Es wurde kein wesentlicher Unterschied festgestellt. Die Werte bewegten sich innerhalb der normalen Grenzen.

	Blutserum mg %	Blasenflüssigkeit mg %
Ca	9,8–12	10–12
K	17–22	16–22
Na	350–360	356–360
P	4,2–6	4,1–6
Cl	570–608	550–607

b) *Gesamteiweiss:* Das Gesamteiweiss der Blasenflüssigkeit schwankte zwischen 4,1 g % und 7,45 g %, das des Blutserums zwischen 4,25 g % und 8,20 g %. Aus der Differenz der Durchschnittswerte des Eiweisses des Blutserums (6,6 g %) und der der Blasenflüssigkeit (5,5 g %) ergab sich ein Unterschied von 1,1 g %.

c) *Elektrophorese:* Die Ergebnisse der Elektrophorese waren folgende. Sowohl im Serum als auch in der Blasenflüssigkeit fanden wir die Gammaglobuline erhöht, während das Albumin erniedrigt war. Der Wert des Al-

umins schwankte bei der Blasenflüssigkeit zwischen 32,2 % und 45,4 %, bei Blutserum zwischen 29,6 % und 45,7 %.

Der Wert des Gammaglobulins schwankte bei der Blasenflüssigkeit zwischen 27,7 % und 42,4 %, beim Blutserum zwischen 24,7 % und 47,4 %.

d) *Aminosäuren:* Sowohl das Blutserum als auch die Blasenflüssigkeit enthielten fast die gleichen 6–10 Aminosäuren, d.h. Alanin, Glykokoll, Glutaminsäure, Valin, Glutamin, Leucin und in geringerem Masse Theonin, Serin, Arginin, Lysin, und Thyrosin. Ihre Fleckenintensität schwankte von 5–30 γ Taurin. Es ist festzustellen, dass die Flecken von Thyrosin manchmal nur im Chromatogramm des Blutserums, manchmal nur in dem der Blasenflüssigkeit auftraten, zu Zeiten aber auch bei beiden gefunden wurden. In jedem Fall waren die Thyrosinflecken kleiner als 5 γ Taurin.

Gruppe C

Diese Gruppe setzte sich aus 17 Kindern zusammen die an akutem Gelenkrheumatismus litten. Die Untersuchung wurde während der Behandlung durchgeführt.

a) *Ionogramm:* Wie bei den beiden obengenannten Gruppen schwankten die Werte innerhalb der normalen Grenzen.

	Blutserum	Blasenflüssigkeit
	mg %	mg %
Ca	10,1–12	9–11
K	20–22	19–21
Na	338–358	350–360
P	5,2–6	4,1–6
Cl	540–550	525–550

b) *Gesamteiweiss:* Das Gesamteiweiss der Blasenflüssigkeit schwankte zwischen 4,6 g % und 6,55 g %, das des Blutserums zwischen 5,6 g % und 8,35 g %. Aus der Differenz der Durchschnittswerte des Eiweisses des Blutserums (6,90 g %) und des der Blasenflüssigkeit (5,5 g %) ergab sich ein Unterschied von 1,40 g %.

c) *Elektrophorese:* Der Wert des Albumins schwankte bei der Blasenflüssigkeit zwischen 36,3 % und 49,6 %, beim Blutserum zwischen 35,9 % und 59,5 %. Der Wert des Gammaglobulins schwankte bei der Blasenflüssigkeit zwischen 15,6 % und 26,5 %, beim Blutserum zwischen 19,9 % und 28,4 %.

d) *Aminosäuren:* Grosse Unterschiede fielen im Vergleich mit der Gruppe B nicht auf. Jedoch beobachteten wir eine Tendenz zur Normalisierung, d.h. eine Erhöhung der Zahl der Aminosäuren und der Farbdichte wie Gruppe B.

Gruppe D

Diese Gruppe setzte sich aus 7 Kindern zusammen, die an akutem Rheumatismus litten. Die Untersuchung wurde nach Abschluss der Behandlung durchgeführt.

a) *Ionogramm:* Wie bei den obengenannten Gruppen schwankten die Werte innerhalb der normalen Grenzen.

	Blutserum mg %	Blasenflüssigkeit mg %
Ca	9,7–12	9,9–12
K	20–21	20,5–22
Na	325–355	320–360
P	3,9–4,5	4,1–6
Cl	550–581,5	550–586

b) *Gesamteiweiss:* Das Gesamteiweiss der Blasenflüssigkeit schwankte zwischen 3,93 g % und 5,95 g %, das des Blutserums zwischen 5,45 g % und 7,45 g %. Aus der Differenz der Durchschnittswerte des Blutserums (6,50 g %) und der der Blasenflüssigkeit (4,92 g %) ergab sich ein Unterschied von 1,58 g %.

c) *Elektrophorese:* Verglichen mit Gruppen B und C fand sich eine weitere Erhöhung des Albumins und eine Erniedrigung des Gammaglobulins.

d) *Aminosäuren:* Die Aminosäuren bewegten sich bei dieser Gruppe fast in den Grenzen des Normalen.

Diskussion

Aus den angeführten Zahlen geht hervor, dass sowohl bei gesunden wie auch bei den Rheumatikern der Wert des Gesamteiweisses in den Blasenflüssigkeit unter dem des Serums liegt. Darüber hinaus sahen wir einen auffälligen quantitativen und qualitativen Unterschied im Eiweiss beider Flüssigkeiten. Bei normalen Kindern findet sich ein Unterschied von 1,85 g % im Eiweiss der Blasenflüssigkeit gegenüber dem Blutserum. Im akuten Krankheitsstadium vor der Behandlung betrug der Unterschied hingegen 1,1 g %. Während der Behandlung stieg er auf 1,4 g % an, um nach Abschluss der Behandlung wieder 1,58 g % zu betragen. Vergleichen wir die obigen Zahlen, so stellt man deutliche Unterschiede zwischen Kranken im akuten Stadium und Gesunden fest. Zeigt sich doch, dass nach Abschluss der Behandlung die Werte sich denen der gesunden nähern, ohne sie jedoch ganz zu erreichen. Wir glauben, die oben erwähnten Resultate wie folgt erklären zu können. Beim akuten Rheumatismus ist die Kapillarpermeabilität gesteigert. Auf Grund dieser Steigerung kommt es zu einer Erhöhung des Eiweisswertes der Blasenflüssigkeit. Unter dem Einfluss der

Therapie tritt eine allmähliche Normalisierung der Permeabilität ein. Ansell, Antonini & Glynn erwähnen den Einfluss von ACTH und Cortison auf die Kapillarpermeabilität für grossmolekulare Verbindungen.

Aus einem Überblick unserer elektrophoretischen Untersuchungen geht hervor, dass das Elektrophoresediagramm bei akutem Gelenkrheumatismus bei Blasenflüssigkeit wie auch beim Blutserum dieselben Veränderungen zeigt. Diese beziehen sich auf Albumin und Gammaglobulin. Während der antirheumatischen Behandlung tritt dann eine Veränderung ein. Im einzelnen besteht im akuten Stadium vor der Behandlung eine Verminderung des Albumins und eine Erhöhung des Gammaglobulins. Vereinzelt haben wir das Gammaglobulin auf das Doppelte der Normalwerte erhöht gefunden. Nach der Besserung des klinischen Bildes kam es zu einer Umkehr der obigen Beziehungen. Eine völlige Normalisierung tritt später ein.

Die Gammaglobuline sind normal im akuten Stadium und während der Behandlung. Nach Abschluss der Therapie sind sie leicht erhöht. Die α_1-Globuline zeigen eine leichte Erhöhung während der Behandlung. Das α_2-Globulin verhält sich normal während aller Krankheitsstadien.

Jackson, Kelly, Smith, Wang & Routh studierten das elektrophoretische Verhalten der Serum- und Plasmaproteine während verschiedener Krankheitsstadien des Rheumatismus. Was Albumin und Gammaglobulin anlangt decken unsere Befunde sich mit denen genannter Autoren. Das α_1- und α_2-Globulin hingegen fanden diese Autoren im akuten Stadium der Krankheit erhöht.

Hinsichtlich der Zusammensetzung der Blasenflüssigkeit bzw. des Serums an Aminosäuren fanden wir keine grossen Unterschiede zwischen beiden. Dies hängt mit der Durchlässigkeit der biologischen Membranen für kristalline Körper zusammen. Auffallend aber ist die zunehmende Verminderung an Aminosäuren, besonders Thyrosin, während des akuten Krankheitsstadiums mit der Tendenz zur Normalisierung nach Abschluss der Behandlung. Die Erklärung dieser Befunde ist schwierig. Bekanntlich wird Thyrosin neben anderen Aminosäuren als Vorstufe von Hormonen angesehen, die auf Grund der Behandlungsergebnisse eine wichtige Rolle in der Pathogenese des akuten Gelenkrheumatismus spielen. Ausserdem können wir erwähnen, dass Thyrosin von geschädigtem kollagenem Gewebe zurückgehalten wird.

Weder Blasenflüssigkeit noch Blutserum zeigen im Ionogramm irgendwelche wesentlichen Unterschiede.

Ergebnisse

1. Das Gesamteiweiss der Blasenflüssigkeit ist erhöht im akuten Stadium, vor der Behandlung des akuten Gelenkrheumatismus. Nach Beginn

der Behandlung vermindert sich der Eiweissgehalt gleichlaufend mit der klinischen Besserung, während nach Abschluss der Therapie das Eiweiss bis fast zu Normalwerten absinkt. Daraus lässt sich auf eine Schädigung der Bindegewebspermeabilität beim akuten Gelenkrheumatismus schliessen.

2. Im Elektrophoresediagramm findet sich während des akuten Stadiums eine Verminderung des Albumins und eine Erhöhung des Gammaglobulins. Mit klinischer Besserung geht eine Erhöhung des Albumins und Verminderung des Gammaglobulins einher.

3. Bei der Chromatographie der Blasenflüssigkeit bzw. des Blutserums zeigt sich eine Verminderung der Zahl und eine Veränderung der Farbintensität der Aminosäuren, besonders des Thyrosin, im akuten Stadium. Nach Abschluss der Behandlung tritt eine Tendenz zur Normalisierung dieser Werte ein.

4. Die Ionogrammwerte bewegen sich während der verschiedenen Krankheitsstadien in normalen Grenzen.

Investigations into a skin test by scarification with cantharidin in children suffering from acute rheumatic fever.

The total protein value of the vesicular fluid in the acute stage of rheumatic fluid is increased before treatment is given. After treatment is instituted the protein level decreases as clinical improvement makes progress, and it returns to almost normal values after treatment is completed. This warrants the conclusion that acute rheumatic fever is associated with a change in the permeability of the connective tissue. The electrophoretic diagram during the acute stage shows a decrease in the albumin and an increase in the γ-globulin fraction. Clinical improvement is associated with an increase in albumin and a decrease in γ-globulin values. Chromatographic examination of the vesicular fluid or the blood serum shows a quantitative decrease and a change in the staining intensity of the amino-acids, especially tyrosine, during the acute stage. After completion of treatment these values tend to return to normal. Ionographic values fluctuate within normal limits throughout the various stages of the affection.

A propos d'une épreuve de cuti-réaction par scarification à l'aide de cantharidine chez des enfants atteints de rhumatisme articulaire aigu.

On note une augmentation du taux des protéines totales dans le contenu de la vessie au moment de la phase aiguë, avant l'institution du traitement du rhumatisme articulaire aiguë. Après l'institution du traitement, le taux des protéines diminue proportionnellement à l'amélioration clinique pour revenir à un niveau pratiquement normal à la fin du traitement. On peut en déduire que le rhumatisme articulaire aigu s'accompagne d'une altération de la perméabilité du tissu conjonctif. Le diagramme de l'électrophorèse que l'on obtient au moment de la phase aiguë, montre qu'il y a diminution du taux des albumines et augmentation de celui des gamma-globulines. L'amélioration clinique va de pair avec un relèvement du taux des albumines et un abaissement de celui des gamma-globulines. La chromatographie du contenu de la vessie ou du sérum fait apparaître une diminution du nombre et une modification de l'intensité de coloration des acides aminés et plus particulièrement de la tyrosine, au cours de la

phase aiguë. Après la cessation du traitement, ces valeurs tendent à se normaliser. Les indices ionographiques se maintiennent dans des limites normales au cours des différents stades de la maladie.

Investigaciones sobre una prueba cutánea mediante escarificación con cantaridina en niños afectos de reumatismo articular agudo.

Las proteinas totales del líquido de la ampolla están aumentadas durante la fase aguda, antes del tratamiento del reumatismo articular agudo. Después de iniciado el tratamiento disminuyen las proteinas totales de modo paralelo a la mejoría clínica, en tanto que después de finalizado aquel la albúmina desciende hasta valores normales. De ello se infiere una alteración de la permeabilidad del tejido conectivo en el reumatismo articular agudo. En el diagrama electroforético se observan, durante la fase aguda, una disminución de la albúmina y un aumento de las gamma-globulinas. Con la mejoría clínica aparecen una elevación de la albúmina y una disminución de las gamma-globulinas. Por cromatografia del liquido de la ampolla, o del suero sanguíneo, se demuestran en la fase aguda una disminución de los valores y una variación de la intensidad colorimétrica de los aminoácidos, principalmente de la tirosina. Después del tratamiento aparece una tendencia a la normalización de estas cifras. Los valores del ionograma oscilan, durante los distintos estadios de la enfermedad, dentro de límites normales.

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Pathogenic Bacteria in the Pharynx and Naso-Pharynx of Hospitalized Children and Their Relation to Clinical Infection

by G. LAURELL, G. TUNEVALL and G. WALLMARK

Infections of the respiratory tract are among the foremost of the diseases encountered in paediatric practice. The causes of these infections are many, including a number of bacterial as well as viral species. In bacterial infections, the species found are on the whole the same as occur in adults: β-haemolytic streptococci (termed streptococci in this paper), pneumococci, *Haemophilus influenzae*, *Staphylococcus pyogenes aureus* (in the following termed staphylococci) and others. However, the infections to which these bacteria give rise in infants and children differ in some respects from the corresponding conditions in adults. The child is far from merely a miniature of the adult as regards infections. Thus streptococci, which in adults commonly produce a typical tonsillitis, may in infancy and early childhood cause a non-characteristic infection known as "streptococcal fever" (8). *H. influenzae*, only to a limited degree and in special conditions capable of establishing infections in adults, is a definitely pathogenic bacterium when present in the respiratory tract of a child. It would also appear that the bacterial flora of the respiratory tract is more variable during the first months of life than later. Coliform bacteria, for instance, are not infrequently found in the respiratory tract of infants below the age of 12 months, but are only rarely present after that age (4). These factors have been given attention to in a number of earlier investigations, but more often they have been overlooked since most studies of childhood infections have been confined to one bacterial species or one age-group only (1, 2, 3, 5, 6, 7, 9, 10, 11).

The aim of the present investigation was to study the incidence in the respiratory tract of children at different ages of the most common pathogenic bacteria, special attention being given to their relationship to respiratory infections. The series studied comprised a total of 780 infants and children, all hospitalized at the Sachs' Hospital for Children during the period September, 1952, to March, 1953. The incidence of the most common

pathogenic bacteria, reported in Section I, was obtained from the series as a whole. Several of the children were, however, swabbed only once. For the study of the relationship between bacterial finding and respiratory infection, 527 children under closer observation were selected (Section II). As was to be expected, the incidence of pathogenic bacteria was higher in this latter group.

Methods

Sampling.—Throat and naso-pharyngeal swabs were taken on admission to the Hospital and subsequently twice weekly. After sampling, the swabs were placed in agar slope tubes for immediate delivery to the laboratory.

Culture.—All samples were inoculated on each of the following media:

(1) Meat infusion agar with 4 per cent horse blood.
(2) Meat infusion agar with 4 per cent horse blood and crystal violet 1:500,000.
(3) Phenol-mannitol agar with 7.5 per cent NaCl according to Chapman.
(4) Meat infusion broth with 2 per cent horse serum.
(5) Meat infusion broth with 2 per cent horse serum and sodium azid 1:3000.

A linear inoculum of a staphylococcal strain (FDA 209 P) was placed across the sample inoculum, for the establishing of satellite phenomena of *H. influenzae*, if present. A blood agar plate was inoculated from the serum azid broth after 48 hours' incubation at 37°C. This was found an effective means of enrichment for pneumococci.

All the plates were incubated aerobically at 37°C and read after 24 and 48 hours. The phenol-mannitol plates were re-examined after a further 24 hours at room temperature. All bacterial species observed were noted. Colonies suspected to be pneumococci, β-streptococci, *H. influenzae*, or *Staphylococcus aureus* were examined as follows:

Pneumococci were typed according to Neufeld's capsule swelling method. Non-typable strains were confirmed with the desoxycholate test.

Streptococci were tested for soluble haemolysin. They were not grouped or typed.

H. influenzae was verified by positive satellite phenomena and Gram-stained smears.

Staphylococci were verified by the coagulase test. A large proportion of the strains isolated were phage typed. (13) These strains were also tested as to sensitivity to penicillin on agar plates containing penicillin in concentrations of 0.1, 1.0, 10, and 100 I.U. per ml, respectively. A heavy inoculum was used. Strains not fully inhibited by 1.0 U. per ml were classed as resistant. The majority of the sensitive strains were inhibited by 0.1 U. per ml.

Results

I. *Incidence of Pathogenic Bacteria in the Series as a Whole*

Pneumococci were isolated from 181 of the 780 children, or 23.3 per cent. The distribution in the different age-groups will be found in Fig. 1, which also gives the age-groups chosen and the age distribution of the series as a

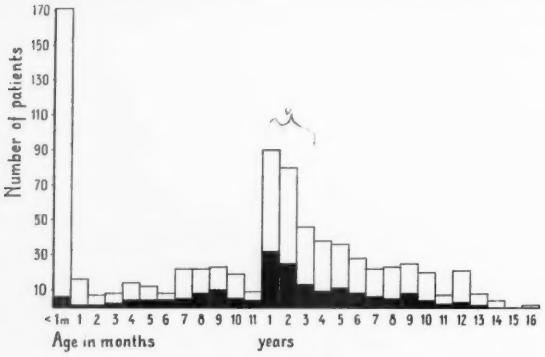

Fig. 1. Incidence of pneumococci at different ages.

whole. As can be seen in the figure, the incidence of pneumococci was appreciably lower in the lowest age-groups than in the others. Pneumococci were isolated from 4.9 per cent of the infants below 4 months, while in the age-group 5 to 47 months they were recovered in 33 per cent of cases, and in 24.9 per cent of the patients over 48 months.

Pneumococcal Types.—A total of 398 strains isolated from 162 children were typed; 358 of them (90 per cent) could be referred to definite types. As is seen in Table 1 a considerable number of types were represented. However, a few types predominated: 22 per cent of the strains belonged to Type 6, 19 per cent to Type 19, 11 per cent to Type 23, and 9 per cent to Type 14. Not infrequently, pneumococci belonging to different types were isolated from consecutive samples in one and the same patient.

Streptococci were isolated from 153 patients or 19.7 per cent of the series. As can be seen in Fig. 2 they were found in 13.9 per cent of infants below

TABLE 1

Distribution of pneumococcal types among 398 strains examined.

Type	Number of strains	%	Type	Number of strains	%
3	17	4.3	18	7	1.8
4	10	2.5	19	75	18.8
6	89	22.4	20	6	1.5
8	8	2.0	21	7	1.8
9	8	2.0	23	43	10.8
11	17	4.3	39	9	2.3
14	37	9.3	Misc.	19	4.8
17	6	1.5	N.T.	40	10.0

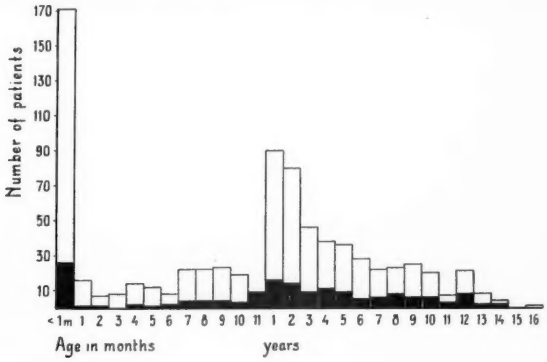

Fig. 2. Incidence of β-haemolytic streptococci at different ages.

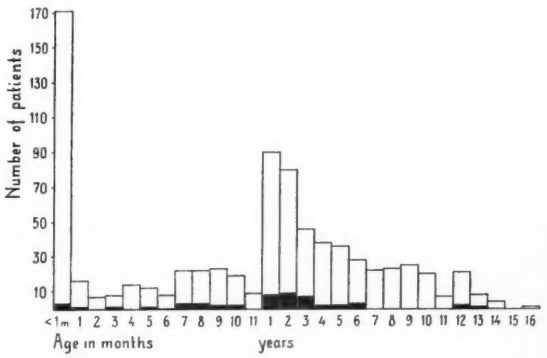

Fig. 3. Incidence of *Haemophilus influenzae* at different ages.

4 months and in 19.7 per cent in the age-group 5 to 47 months, while in children over 48 months they were found in as high a proportion as 28.3 per cent.

Haemophilus influenzae was, as can be seen in Fig. 3, of low incidence, being found in 51 cases or 6.5 per cent. Below the age of 4 months, *H. influenzae* was isolated from only 2.9 per cent of infants. Between 5 and 47 months, the incidence was 10.1 per cent, and over 47 months 4.3 per cent.

Staphylococci.—Coagulase-positive staphylococci were isolated from 393 of the 780 children, i.e. 50.7 per cent. The incidence in the different age-groups is given in Fig. 4.

Staphylococci were most frequent in the lowest age-groups, being there between 70 and 80 per cent. In older children, staphylococci were recovered from between 30 and 50 per cent of cases. Thus, staphylococci were the potentially pathogenic bacteria most commonly present in the series studied.

Phage types and penicillin sensitivity.—A total of 449 strains isolated

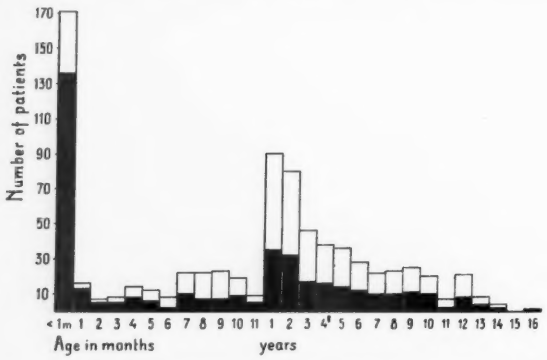

Fig. 4. Incidence of *Staph. pyogenes aureus* at different ages.

from 195 children were examined. The same phage type was frequently noted in consecutive samples from the same patient. Only one strain of each phage type from one and the same patient is included in the analysis. This selected material embraces 249 strains from 195 children. The distribution of the various phage types and phage groups will be found in Table 2.

TABLE 2

Phage types and sensitivity to penicillin among 249 strains of Staph. aur.

Phage group	Phage pattern	Total no.	No. resistant	Resistant, %
I	KS6+(10)[a]	17	3	17.6
II	3B/3C (1A)	7	2	
	3B/3C/51 (1B)	3	—	
	3B/3C/51 W.	43	29	
Total		53	31	58.5
III	6/47/819/1034+(2A)	10	4	
	6/47+(2C)	9	9	
	47/819/1034+(5B)	8	8	
	6/47/1034+(11A)	6	4	
	47/1034+(11B)	4	4	
	Misc. reactions	20	11	
Total		57	40	70.2
	166/155 (12)	19	3	
	166/155 W	18	5	
	166 W	14	1	
Total		51	9	17.6
	Non typable	71	38	53.5
GRAND TOTAL		249	121	48.6

[a] The number in brackets denotes the corresponding phage type previously referred to. The strains designated as KS6+ are closely related to strains of phage pattern 52/80 (Group I) (14).

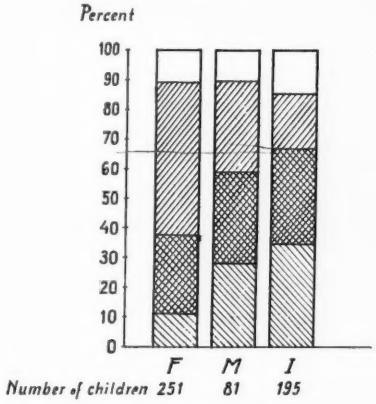

Fig. 5. Bacterial incidence in the three clinical groups. (F = free from infection, M = moderate infection, I = hospitalized for infection.)

Of the strains examined, 6.8 per cent belonged to phage Group I, 21.3 per cent to Group II, 22.9 per cent to Group III, and 20.5 per cent were completely or partially lysed by the phages 166 and 155. In test dilution, the phages used failed to lyse 28.5 per cent of the strains. No clear predominance of any particular type was noted.

Of the strains examined, 48.6 per cent were resistant to penicillin. In agreement with earlier observations, the resistant strains predominated in phage Group III, although their incidence was also high in phage Group II.

II. *Relation between the Presence of Potentially Pathogenic Bacteria and Clinically Manifest Infection*

For this study, 527 children who had been under sufficiently strict observation were selected. They were divisible into three groups: Group 1 (251 children), comprising children apparently free from infections; Group 2 (81 children), in which, although the patients had not been hospitalized because of infection, the case histories or physical examination were suggestive of infection of the respiratory tract shortly before admission or during hospitalization; Group 3 (195 children), in which infection of the respiratory tract was the direct reason for hospitalization. The results of this analysis will be found in Fig. 5.

As was to be expected, the incidence of pneumococci, streptococci and *H. influenzae* was appreciably higher among children with manifest infection than among those free from infection. It should be noted that two of the three bacterial species listed above coexisted in 27 children, and all three species in 4 children. These cases were fairly evenly distributed among the three groups.

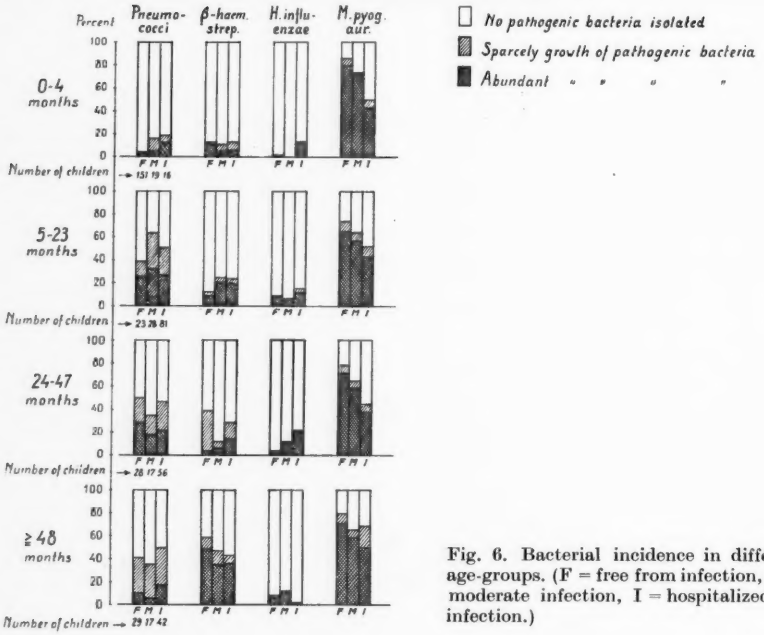

Fig. 6. Bacterial incidence in different age-groups. (F = free from infection, M = moderate infection, I = hospitalized for infection.)

The opposite applies to staphylococci. A more or less heavy growth of staphylococci was demonstrated in the pharynx and nasopharynx of 76.3 per cent of patients lacking clinical signs of infection. The corresponding figure for Group 2 was 61.6 per cent, and for Group 3 (infection group) 57.7 per cent. Furthermore, the presence of pneumococci, streptococci, or *H. influenzae* appeared to lessen the likelihood of finding staphylococci in that child, and vice versa. Staphylococci were present in 75 per cent of all samples in which the other three bacterial species were absent, but were recovered from only 57 per cent of samples containing one or more of those three species.

The incidence of the four bacterial species in the three clinical groups in four different age-groups will be found in Fig. 6.

Here, too, the high incidence of staphylococci in the whole series was striking, as was the predominance of staphylococci in the group lacking clinical evidence of infection. It will also be seen that the high incidence in the infection group of the other pathogenic bacteria studied applied only to certain species in certain age-groups. Otherwise, the distribution of the bacteria was fairly uncharacteristic, the proportion of clinically healthy carriers of pathogenic bacteria being fairly large. Pneumococci were en-

countered most frequently, but in the infection group their incidence was significantly higher only in the infants below 4 months. Streptococci came next in order of frequency; these bacteria were more common in the infection group between the ages of 5 and 47 months. *H. influenzae* occurred most frequently in the infection group in all but the children over the age of 48 months.

It may be of interest to note that the incidence of the pathogenic bacteria studied showed no noteworthy seasonal variation during the period of observation.

Relation between Bacterial Species and Type of Infection

It appeared worthwhile to study the correlation between the type of infection and the incidence of the different bacterial species. The results of an analysis of 117 cases with clearly defined clinical diagnoses, in which only one pathogenic bacterial species was found, are given in Table 3.

TABLE 3

Bacterial findings in 117 cases of clinically manifest infection.

Type of infection	Bacterial species			Number of cases
	Pneumococci	Streptococci	*H. influenzae*	
Rhinopharyngitis	25	10	14	49
Tonsillitis	8	1	2	11
Bronchitis	13	6	7	26
Pneumonia	9	6	4	19
Lymphadenitis (cervical)	0	1	0	1
Otitis	6	2	1	9
Sinusitis	1	1	0	2

On the whole, then, pneumococci, streptococci, and *H. influenzae* appeared to be present in the different types of infection roughly in proportion to their incidence in the series as a whole. Only in two respects was there any deviation from this rule: pneumococci predominated in otitis, and there was a very striking preponderance of pneumococci in cases characterized clinically as tonsillitis.

Discussion

The number of cases in which no pathogenic bacteria were found at any time during the period of observation may serve as a measure of the reliability of the sampling and culture methods used. These cases comprised only about 10 per cent of the whole series.

Pneumococci were relatively rare in the lowest age-group but, on the other hand, those infants harbouring pneumococci had frequently clinically manifest infection. This bears out earlier observations as to the predilection of pneumococcal infection for the very young. It was of particular interest that in these infants pneumococci were recovered appreciably more frequently than streptococci in cases showing the features characteristic of tonsillitis; this has been observed earlier by the present authors. It would appear, then, that the tonsillitis reaction is not necessarily connected with streptococci but, rather, derives from a certain mode of reaction between the bacteria and the tissue involved. This reaction seems to be established earlier in the infant by pneumococci than by streptococci.

The type-distribution of the pneumococci did not differ from that of earlier Stockholm series. Types 6, 14, 19, and 23 together accounted for 61 per cent of all typed strains. No definite preponderance of any one type was demonstrable in the infection cases.

Streptococci were also found more frequently in the older children. Only in the two intermediary age-groups, from 5 to 47 months, was the presence of these bacteria more closely correlated with manifest infection.

H. influenzae was isolated fairly rarely, in only 6 per cent of the cases. However, this bacterium was closely linked to the infection group right up to the age of 4 years.

The high incidence of double or triple bacterial infections should be noted, prompting caution when considering aetiology and in the choice of treatment for the infections of childhood.

In this, as in earlier series studied by the present authors and others, the incidence of staphylococci in the upper respiratory tract was considerable, approximately 50 per cent in the whole material. In the group under closest observation in which several samples were taken, the incidence was even higher, or 61.0 per cent. It was most prevalent in the lowest age-groups. Had samples been taken from the vestibule of the nose, it seems likely that the incidence would have been even higher. Of the strains examined, 52 per cent belonged to phage Groups I, II, and III, and 20 per cent to the Group 166/155; no clear predominance of any one type was noted. The incidence of penicillin-resistant strains in phage Groups I, II, and III was 17 per cent, 58 per cent, and 70 per cent, respectively. The proportion of resistant strains in phage Group III agrees with earlier observations, while that in phage Group II was unusually high.

As was to be expected, pneumococci, streptococci, and *H. influenzae* were recovered more frequently from the pharynx and naso-pharynx of patients with clinically manifest infection than from those free from infection. The opposite, however, applies to staphylococci, the incidence here

being higher in the children without clinical signs of infection. In other words, the presence of staphylococci in a sample appears to lessen the likelihood of finding the other bacterial species, and vice versa. The clinically manifest respiratory infections were correlated with the presence of pneumococci, streptococci, and *H. influenzae*, but the correlation with staphylococci was negative. Whether or not this should be interpreted as a competitive phenomenon, and if so which of the possible factors is of primary importance, is an open question.

The results of the present investigation illustrate clearly the difficulty of assessing the role of staphylococci in respiratory infections solely by means of comparative analyses of incidence. According to a paper published recently (12), accurate correlation of the pathogenicity calls for a more penetrating analysis of the toxin and enzyme systems of staphylococci.

Summary

The incidence of potentially pathogenic bacteria was noted in throat and naso-pharyngeal samples from all the 780 infants and children hospitalized at a children's hospital during a period of 7 months. Pneumococci were isolated from 23.2 per cent of the patients, β-haemolytic streptococci from 19.7 per cent, *H. influenzae* from 6.5 per cent, and *Staph. pyogenes aureus* from 50.7 per cent. Pneumococci, β-streptococci, and *H. influenzae* all showed a positive correlation with the presence of clinically manifest respiratory infection, whereas the opposite applied to *Staph. aureus*. Pneumococci were most frequently correlated with clinical infection in the lowest age-group (below 4 months), β-streptococci in somewhat older subjects (5 to 47 months), while infections caused by *H. influenzae* occurred approximately equally often in all the age-groups up to 4 years. Mixed infections were relatively common. No definite predominance of any one bacterial species in any one type of infection was noted, with the exception of the preponderance of pneumococci in otitis and, to be emphasized, in tonsillitis.

The presence of *Staph. aureus* appeared in some measure to preclude the simultaneous presence of other potentially pathogenic bacteria or vice versa. No definite predominance of any one phage type was noted. Of the strains examined, 48.6 per cent were resistant to penicillin. The incidence of resistant strains was 17.6 in phage Group I, 58.5 per cent in phage Group II, and 70.2 per cent in phage Group III.

Les bactéries pathogènes du pharynx et du rhino-pharynx chez les enfants hospitalisés et leurs rapports avec les infections cliniques.

L'incidence des bactéries potentiellement pathogènes a été relevée durant sept mois par l'examen d'échantillons prélevés du pharynx et du rhino-pharynx de 780 enfants et nourrissons hospitalisés dans une clinique pédiatrique. La présence de pneumocoques a été relevée dans 23,2 % des cas; celle de streptocoques bêta-hémolytiques, dans 19,7 % des cas; celle d'H. influenzae dans 6,5 % des cas et celle de staphylocoques pyogènes dorés dans 50,7 % des cas. On a constaté l'existence d'une corrélation effective entre la présence de pneumocoques, de streptocoques bêta ou d'H. in-

fluenzae et celle d'une infection respiratoire cliniquement manifeste; cette corrélation ne s'est par contre pas vérifiée avec le staphylocoque doré. Il est apparu que la présence du pneumocoque était le plus souvent en relation avec les infections cliniques intéressant les malades de la plus petite catégorie d'âge (en dessous de 4 mois); le streptocoque bêta fut principalement retrouvé chez des sujets un peu plus âgés (de 5 à 47 mois) tandis que les infections dues à l'H. influenzae furent observées dans des proportions à peu près équivalentes dans toutes les catégories d'âge jusqu'à 4 ans. Les cas d'infections mixtes furent relativement fréquents. Aucune prédominance particulière d'un agent bactérien donné pour l'un ou l'autre type d'infection ne fut observée; la seule exception concerne le pneumocoque dans les otites et, il y a lieu de le souligner, dans les amygdalites. Il semble que la présence du staphylocoque doré ait exclu dans une certaine mesure celle d'autres bactéries potentiellement pathogènes. Aucune prédominance de l'un ou l'autre type de phage n'a été observée. 48,6 % des souches étudiées se sont révélées résistantes à la pénicilline. L'incidence des souches résistantes fut de 17,6 % pour les phages du groupe I, de 58,5 % pour les phages du groupe II et de 70,2 % pour les phages du groupe III.

Pathogene Bakterien in Pharynx und Nasopharynx bei ins Krankenhaus zugelassenen Kindern und ihre Beziehung zur klinischen Infektion.

Das Vorkommen potentiell pathogener Bakterien wurde in Abstrichen aus dem Hals und dem Nasopharynx von allen 780 Säuglingen und Kindern, welche während einer 7monatigen Zeitspanne in ein Kinderhospital zugelassen worden waren, festgestellt. Pneumokokken wurden bei 23,2 % der Kranken isoliert, beta-haemolytische Streptokokken bei 19,7 %, H. influenzae bei 6,5 % und Staph. pyogenes aureus bei 50,7 %. Pneumokokken, beta-Streptokokken und H. influenzae standen immer in einer positiven Beziehung zu einer gleichzeitigen klinisch manifesten Infektion der Atemwege, im Gegensatz zum Staph. aureus. Pneumokokken waren am häufigsten in einer klinischen Infektion bei der jüngsten Altersgruppe (unter 4 Monaten) beteiligt, beta-Streptokokken bei etwas älteren Patienten (5–47 Monate), während Infektionen mit dem H. influenzae in annähernd gleichem Masse alle Altersgruppen bis zu 4 Jahren betrafen. Mischinfektionen waren verhältnismässig häufig. Kein deutliches Vorherrschen irgendeiner Bakterienart bei irgendeinem Infektionstypus wurde beobachtet mit Ausnahme eines vorwiegenden Anteils von Pneumokokken bei Otitis und, was betonenswert ist, Tonsillitis. Die Anwesenheit von Staph. aureus schien gewissermassen die gleichzeitige Gegenwart anderer potentiell pathogener Keime auszuschliessen. Kein eindeutiges Vorherrschen irgendeines Phagetypus wurde beobachtet. Von den untersuchten Bakterienstämmen waren 48,6 % penicillinresistent. Das Vorkommen resistenter Stämme betrug 17,6 % in Phagegruppe I, 58,5 % in Phagegruppe II und 70,2 % in Phagegruppe III.

Bacterias patógenas en la faringe y nasofaringe de niños hospitalizados y su relación con la infección clínica.

La incidencia de las bacterias patógenas potenciales fué observada en muestras faríngeas y nasofaríngeas de todos los 780 lactantes y niños hospitalizados en un hospital infantil durante un período de 7 meses. Se aislaron neumococos de un 23,2 % de los pacientes; estreptococos β hemolíticos de un 19,7 %, Hemophilus influenzae de un 6,5 % y estafilococos áureos piógenos de un 50,7 %. Los neumococos, los estreptococos β y H. influenzae, presentaron en su totalidad una correlación positiva con la

presencia de la infección respiratoria manifiesta clínicamente, mientras lo opuesto se aplica a los estafilococos áureos. Los neumococos estaban más frecuentemente correlacionados con la infección clínica en el grupo más jóven (de menos de 4 meses), los estreptococos β en sujetos algo mayores de edad (5 a 47 meses), mientras que las infecciones causadas por H. influenzae se presentaron aproximadamente con igual frecuencia en todos los grupos hasta los 4 años de edad. Las infecciones mixtes fueron relativamente comunes. No se observó un predominio determinado de alguna de las especies de bacterias de cualquiera de los tipos infecciosos, salvo la preponderancia de los neumococos en la otitis y, con especial mención, en la tonsilitis. La presencia de estafilococos áureos pareció en cierto punto excluir la presencia simultánea de otras bacterias patógenas potenciales. No se ha observado la predominancia definida de cualquiera de estos tipos de bacteriófagos. Un 48,6 por ciento de las cepas examinadas fué resistente a la penicilina. La incidencia de las cepas resistentes, por grupo de bacteriófagos, fué de un 17,6 por ciento en el Grupo I, 58,5 por ciento en el Grupo II y 70,2 por ciento en el Grupo III.

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Infections with Poliovirus Types 2 and 3 in Day Nurseries and an Orphanage

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It is by now well established (2–6; 8–11) that poliomyelitis is a highly contagious infection that usually spreads to most susceptible individuals living in close contact with each other, such as members of the same family, children attending the same nursery school, etc. This pattern may be studied only by virological methods as the infection in most cases is inapparent or associated with a clinically nonspecific minor illness.

These facts are again illustrated by the results of the present study of two institutional outbreaks of poliomyelitis infections which occurred in Stockholm during the fall of 1955. The first environmental investigation was prompted when in September two paralytic cases occurred in a day nursery a few days apart. One month later a similar study was started in another part of the city at a combined orphanage and day nursery where another paralytic case had occurred about a month previously and where a fresh case of aseptic meningitis suggested that the infection was still spreading. Poliov ruses Types 2 and 3, respectively, were recovered from these outbreaks.

It may be mentioned that none of the persons studied during the present investigation had been vaccinated against polio, nor were they given gamma globulin.

Epidemiology

Only a few paralytic cases were registered in Stockholm during the fall of 1955. If persons belonging to the two outbreaks studied are excluded, there was only one paralytic case with onset in August, 6 in September, and 10 in October. The relatively few poliovirus strains isolated from these

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or other patients at the Hospital for Infectious Diseases (persons belonging to the present study again excluded) were shown to be distributed between all three types. Thus 2 Type 1 strains were recovered from a total of 31 suspected cases (with various final diagnoses) with onset in August, 1 Type 1 and 3 Type 2 from 64 patients in September, and 3 Type 2 and 8 Type 3 from 98 cases in October. Apparently there was no reason to believe that the viruses causing the outbreaks to be described were at the same time very common in the rest of the population.

Outbreak I.—The first outbreak to be described occurred at a well equipped day nursery meant preferably for the children of self-supporting women in a modern part of Stockholm. The children were all living in the neighbourhood in modern apartment houses. They attended the nursery in daytime only, i.e. between 7 a.m. and 6 p.m. Three meals a day were served, one of them from a collective restaurant which also served many of the residents of the 58 apartments of the 8 floor house. The age of the 33 children attending the nursery varied between 3 and 6 years. The staff comprised 5 women; 6 persons were employed in the kitchen of the restaurant.

The first case of poliomyelitis among the nursery children occurred on September 13, 1955 when a 6-year-old girl came down with prodromal symptoms, 4 days later followed by signs of meningeal irritation. A paralysis of the left leg was found when the child was already in convalescence. Poliovirus Type 2 was isolated from a stool specimen taken on September 24. The second case, a 3-year-old girl with paralysis of the neck and shoulders, followed on September 23. Both were hospitalized. No other cases with significant symptoms from the central nervous system occurred, neither among the nursery children nor among their relatives at home or among the persons working or living in the apartment houses. It might be mentioned also that a technical investigation performed by the sanitary personnel of the Stockholm Board of Public Health did not disclose any defects of the water supply or sewage system; no coli were found in the tap water.

Twenty-one of the 31 remaining nursery children were voluntarily hospitalized on September 29 for clinical investigation, the others were isolated at home for a period of three weeks. Stool specimens were procured about October 1 from all nursery children as well as from the relatives living together with them (10 children and 47 adults). Stools were also collected from the 5 staff members, from the 6 persons working at the restaurant kitchen and, finally, from 4 adults who were living in the apartments of the house and were the only residents showing signs of minor illness at the time of the investigation. Repeated specimens were taken over a period of about six weeks. Blood specimens were drawn from most of these persons on about October 1 as well as about two and six weeks later. All these persons were also questioned and investigated for signs of illness.

Outbreak II.—As mentioned above, the second environmental study was performed at a combined orphanage and day nursery in another part of Stockholm. The localities were quite modern and sanitarily well equipped here too. The orphanage contained 22 children aged 1–3 years. The day nursery was divided in three sections containing respectively 11 children aged 6–18 months, 14 with an age of 2–3 years and 12 with an age of 4–6 years. These children were all living in modern apartment houses in the neighbourhood. The staff of the orphanage comprised 21 women, that of the day

nursery 7 women. By and large, each of these persons was working only for one of the groups of children mentioned above. One nurse worked alternatively at all sections, however, and 6 other employees also had contacts with all categories of children: the two women working in the collective kitchen (from which 3 meals a day were served to all children and personnel), 3 maids and 1 janitor. The various categories of children were kept in separate locations and direct contacts between them was usually avoided. Those children who arrived especially early in the morning (6.30 a.m.) were kept together in one room for an hour, however. When outdoors, the various groups (except infants) were not kept apart. Furthermore, several pairs of siblings attended separate sections. Thus 3 pairs (2 of which contained a poliovirus excretor) belonged to the youngest and the middle group and 3 pairs (1 poliovirus-positive) to the two oldest groups.

It should be noted also that there was considerable intermingling between the staff members. Moreover, the mother of one of the virus-positive pairs was a nurse working at the orphanage.

The paralytic index case occurred at the 2–3 years section of the day nursery. It was a girl about two years of age, who came down with fever on September 23. Three days later she developed signs of meningeal irritation and weakness of her right leg. Poliovirus Type 3 was recovered from a stool specimen obtained on September 29. It is possible, however, that poliovirus Type 3 was already the cause of a facial paralysis found somewhat earlier in one of the infants. The paralysis was noted some time between September 2 and 21 when the child was isolated in her own home due to signs of upper respiratory disease. No adequate specimens were available for laboratory tests but a serum taken from the 10 months old child on October 10 was found to contain neutralizing antibodies against poliovirus Type 3 but none against the others. On October 18 a 4.5-year-old girl from the oldest section of the nursery got fever and showed signs of meningeal irritation. She was hospitalized the next day and a diagnosis of aseptic meningitis was established. A stool specimen from October 25 contained poliovirus Type 3. No other children developed significant symptoms from the central nervous system.

The environmental study at the day nursery and the connected orphanage was started on October 21, as a complement to the investigation at the other day nursery mentioned above. Again many of the remaining day nursery children (29 out of 35) and three of the orphanage children were hospitalized. The other children were isolated at home or at the orphanage for three weeks. The day nursery was closed during this period and no new children were admitted to the orphanage. A 44-year-old nurse from the orphanage was also hospitalized because she had suffered from headache and fever about October 1. She was found to have an aseptic meningitis but no virus was recovered.

Stool specimens were taken from all children and personnel according to a schedule similar to that mentioned above for the other day nursery. Very few blood specimens were obtained, however. No family members were investigated this time.

Virological Methods

Specimens of stools and sera were stored at −25°C until tested. Virus isolations were performed, either in roller tube cultures of human embryonic lung or, in most cases, in roller tube cultures of HeLa cells (12). Only the first series of stool specimens from the first day nursery was tested in lung cultures. When HeLa cells were employed

the inoculum was doubled (0.2 ml per each of three tubes) and the medium was changed following three hours of incubation in the roller drum in order to minimize toxic effects. Bovine amniotic fluid with 0.5 per cent Bactotryptose and antibiotics was employed as a medium. It should be mentioned that in an experiment preliminary to the present isolations our HeLa cells were, at this time and with the use of this technique, found to be at least as sensitive as the lung cultures to minimal doses of stool viruses. Thus, out of 20 stool specimens which in the primary isolation tests had caused cytopathic changes in only a fraction of the lung cultures inoculated, 16 were in a repeated test positive in lung cultures (81 tubes positive out of 198) and 19 in HeLa cultures (134 tubes positive out of 199). In similar previous experiments with a slightly different technique the HeLa cells were found to be significantly inferior (12).

Each virus strain isolated was identified by neutralization with type-specific serum.

Late sera from those persons from whom no virus was isolated were screened for neutralizing antibodies against the Brunhilde, Lansing and Leon strains by testing undiluted serum against 100 ID_{50} of virus.

Results

Outbreak I

Not less than 31 of the 33 children at the first place were found to excrete poliovirus Type 2. Furthermore, late sera from the two remaining children neutralized this type of virus. As might be expected other persons in intimate contact with the nursery children, at the nursery or in their homes, were very often found to excrete the virus. Thus 2 of the 5 staff members provided positive stool specimens, and likewise 7 of the 10 siblings and 10 of the 47 adults living together with the nursery children excreted virus. On the other hand, none of the kitchen personnel excreted Type 2 virus, and it was not recovered from the few adult residents of the apartment house who were examined. An infection with poliovirus Type 3, diagnosed in one of the residents, was obviously contracted somewhere else.

The results of neutralization tests on late sera suggest that some of the virus-negative persons did actually escape the infection. Thus 2 of the staff members, 10 adults at home (all but one with virus-positive children) but none of the siblings lacked antibodies against Type 2 virus. The same was true for 2 of the employees in the kitchen. The 3 residents examined all had Type 2 antibodies. It may be noted, however, that most (12 out of 14) of these persons who did not develop neutralizing antibodies against Type 2 virus had antibodies against either Type 1, Type 3 or both; only two individuals (a nurse and a father of two virus-positive children) lacked antibodies against all three types of poliovirus.

Outbreak II

The recovery rate of poliovirus Type 3 at the combined nursery and orphanage was somewhat lower than that of Type 2 virus at the first day

nursery. It should be emphasized, however, that a longer time, not less than about a month, had elapsed since the onset of the paralytic index case when the present environmental investigation was started. It is thus probable that the excretion state had ceased for several infected individuals. On the other hand, the appearance of a fresh case of aseptic meningitis just before the present investigation suggests that new infections were still occurring.

Altogether 54 per cent of the children were found to excrete poliovirus Type 3. Sixteen of the 22 orphans were thus poliovirus-positive, and at the day nursery 4 of the 11 infants, 3 of the 14 children in the 2–3 year group and 9 of the 12 oldest children provided positive stool specimens. Only 2 women among the personnel (33 tested out of 34) excreted poliovirus Type 3. Both worked at the orphanage.

Again the outcome of neutralization tests suggests that some persons did escape infection. Thus 4 of 5 virus-negative children (the only ones from whom a late serum was available) lacked antibodies against all three types of poliovirus at the end of this study (the fifth child tested had antibodies against all three types). Nine of 31 virus-negative adults also failed to develop Type 3 antibodies. It may be noted that 5 of them had antibodies against Type 2 virus and 1 against Type 1, however.

Duration of poliovirus excretion

The beginning of the excretor state may be estimated only for the paralytic cases where the onset of disease may be employed as an objective point of reference. As discussed below the various "minor illnesses" encountered among the other virus excretors may hardly be ascribed to the poliovirus infection with any degree of certainty, however. The length of the individual carrier state may thus not be accurately estimated.

This is obvious especially for the Type 3 outbreak where other virus infections were demonstrably frequent at the same time (se below) and, furthermore, the fresh polio infections were probably scattered over a month at least. As the investigation was not started until about a month after the index case early short-time excretors may have been missed entirely. The Type 2 outbreak, on the other hand, was apparently more uniform. As a consequence of these considerations the figures given below are based upon the onset of the index cases.

At the first outbreak all but one of the 50 Type 2 excretors were positive in the first stool specimen obtained. One mother had, however, two negative specimens followed by a positive one on October 15. Only in one case was a negative specimen obtained between positive ones. Eighty-five per cent of

the poliovirus excretors provided positive specimens still 3–4 weeks (38/45), as well as 4–5 weeks (38/44) after onset of the index case. The frequence decreased to 25 per cent (11/45) for specimens taken after 7–9 weeks.

Of the 34 Type 3 excretors at the combined nursery and orphanage 4 were polio-negative in the first 1–2 specimens delivered but positive in later ones; one of these persons and 6 others had polio-negative specimens surrounded by positive ones. About 50 per cent of those who excreted poliovirus Type 3, at one time or another, delivered positive stools about 5–6 weeks (15/29) as well as 6–7 weeks (12/26) after the index case; 7 per cent (2/27) still after 10–11 weeks.

These findings provoke some comment. Although application of quarantine for 3 weeks, as recommended by WHO, may perhaps reduce the spread of virus in the community it seems obvious, as pointed out by others (4), that no drastic effect may be expected by such a measure. Most virus excretors remain positive for considerably longer periods of time. There are indications that this may be true especially for children (4, 12) who certainly also disseminate the virus more effectively.

Isolation of other agents

The outbreak of poliovirus Type 2 infections was quite uniform. The single recovery of poliovirus Type 3 from one of the residents of the apartment house was mentioned above. Furthermore, two cytopathogenic agents other than polio- or adenovirus were recovered which have so far not been typed. One of them was isolated on November 10 from a healthy mother, the other on October 31 from a father who simultaneously developed an aseptic meningitis. In both cases the corresponding nursery children excreted poliovirus Type 2, however.

Among the children at the combined nursery and orphanage the picture was considerably more complex. Thus 3 cases of mumps occurred during the observation period: the first on October 12 at the 2–3 year section, the second on November 13 among the infants and the last (complicated with aseptic meningitis) on November 25 at the 4–6 year section. No viruses other than poliovirus Type 3 were recovered from the infants or the oldest group at the day nursery (with the exception of a nontyped agent found in a very late (November 10) stool specimen from a child who previously had excreted poliovirus Type 3). On the other hand the 2–3 year section of the day nursery was found to contain 3 excretors of adenoviruses (2 Type 2 and 1 Type 3) and 2 donors of nontyped agents. Twelve of the orphans excreted adenoviruses at one time or another but here other types were found (Types 1 and 5) and 7 of the cases had poliovirus Type 3 in other stool specimens.

It should be mentioned, finally, that many children harboured potentially pathogenic bacteria in the nasopharynx. Thus, on admission to Hospital, 7 of 57 children had β-hemolytic streptococci, 4 had *Haemophilus influenzae*, 11 pneumococci and 4 *Staphylococcus aureus* (G. Tunevall, personal communication). There was no great difference between the two groups in this respect.

Clinical Considerations

The majority of the investigated contacts involved in the two outbreaks, whether poliovirus-positive or not, had experienced one or sometimes several episodes with minor symptoms during the weeks between the onset of the paralytic index cases and the beginning of the present environmental investigations. Thus only 10–20 per cent of the children had shown no symptoms of disease whereas 60–70 per cent had experienced signs of upper respiratory disease, 50–60 per cent had had fever and 20–40 per cent headache. Actually, 8 (only 5 of which were poliovirus-positive) out of 50 investigated children had elevated cell counts in their cerebrospinal fluid (more than 5 leucocytes per mm^3) although they had not demonstrated clinical signs of meningeal irritation. Gastrointestinal symptoms such as vomiting and diarrhea were much more common during the second outbreak (at the combined orphanage and day nursery). In the latter case about half of the children as well as of the personnel had suffered from diarrhea and 20–30 per cent had had vomiting whereas the corresponding figures for the children involved in the Type 2 outbreak were only 2 and 5 per cent, respectively. Twelve per cent of the children in the second outbreak had also suffered from conjunctivitis. It is known that at least one type of adenovirus (Type 3) may cause both conjunctivitis (1) and gastrointestinal disorders (7) in addition to respiratory disease. However, there was in the present material as little correlation between the recoveries of adenoviruses and these symptoms as between the recoveries of polioviruses and any of the other symptoms. It seems plausible, furthermore, that some of the episodes encountered were due to the bacterial pathogens that were also demonstrated. The present investigation thus well illustrates the difficulties that are commonly met with in attempts to ascribe uncharacteristic symptoms to infections with a certain pathogen. No definite conclusions may be drawn in this respect regarding any of the outbreaks studied, particularly not for the outbreak of poliovirus Type 3 infections.

Summary

In the fall of 1955, when the incidence of poliomyelitis was low in Stockholm, two institutional outbreaks of poliovirus infections were studied. At one day nursery,

where two paralytic cases had occurred one and two weeks earlier, 31 of the 33 children and 2 of the 5 members of the personnel excreted poliovirus Type 2. The infection was also widespread among the household contacts; thus 7 of 10 siblings and 10 of 47 adults were virus-positive. Eighty-five per cent of the virus excretors provided further positive stool specimens still 4–5 weeks after onset of the first paralytic case; 25 per cent still after 7–9 weeks.

At the other institution, a combined day nursery and orphanage, the paralytic index case had occurred a month earlier, followed by a case of aseptic meningitis just before this investigation. Thirty-two of the 59 children and 2 members of the personnel of 34 adults were found to excrete poliovirus Type 3. Here 50 per cent of the virus excretors provided poliovirus-positive specimens 6–7 weeks after onset of the paralytic index case; 7 per cent still after 10–11 weeks.

Infections with other agents were also discovered among the children studied. Bacterial pathogens were thus common in both outbreaks; and adenoviruses Types 1, 2, 3 or 5 were recovered at one or several occasions from 15 children belonging to the second outbreak. The many episodes of minor illness met with among the persons studied could not be definitely correlated to any of the pathogens encountered.

Infections du polio-virus types 2 et 3 dans des crèches et dans un orphelinat.

En automne 1955, lorsque l'incidence de poliomyélite était basse à Stockholm, on a examiné des infections du polio-virus survenues dans deux institutions. Dans une crèche où 2 cas de paralysie étaient signalés 2 et 3 semaines auparavant, il y avait 31 sur 33 enfants, et 2 sur 5 membres du personnel, qui avaient une excrétion du polio-virus type 2. L'infection était donc très répandue parmi les pensionnaires et le personnel; ainsi, 7 sur 10 enfants, et 10 sur 47 adultes avaient une réaction positive du virus. 85 % des individus avec une excrétion du virus produisaient encore des spécimens de selle positifs 4 à 5 semaines après le début des premiers cas de paralysie, tandis qu'après 7 à 9 semaines, ce pourcentage était de 25 %. Dans l'autre institution, une crèche combinée avec un orphelinat, un cas avec des indications pour une paralysie avait lieu un mois plus tôt et il était suivi d'un cas de méningite aseptique, survenu juste avant cette investigation. Chez 32 sur 59 enfants, et chez 2 sur 34 membres du personnel, on a trouvé une excrétion du poliovirus type 3. Ici, 50 % des individus avec une excrétion du virus produisaient des excréments avec du poliovirus positif 6 à 7 semaines après le début du cas de paralysie signalé, tandis que 10 à 11 semaines plus tard, ce pourcentage s'élevait encore à 7 %. Parmi les enfants examinés, on a également trouvé des infections d'autres agents. Ainsi, les microbes pathogènes dans les deux épidémies étaient courants, et à une ou plusieurs occasions, les adrénovirus des types 1, 2, 3 ou 5 étaient éliminés de 15 enfants appartenant à la deuxième épidémie. Les nombreuses épisodes de maladies d'importance secondaire, constatées chez les individus examinés, ne pouvaient etre mises définitivement en corrélation avec aucun des microbes pathogènes rencontrés.

Infektionen mit Poliovirus vom Typus 2 und 3 in einem Kindergarten und Waisenhaus.

Im Herbst 1955, wenn Poliomyelitisinzidenz in Stockholm gering war, wurden zwei Ausbrüche von Poliovirusinfektion in Anstalten studiert. In einem Kindergarten, in dem zwei paralytische Fälle eine und zwei Wochen früher vorgefallen waren,

schieden 31 unter den 33 Kindern und 2 unter den 5 Mitgliedern des Personals Polioviren vom Typus 2 aus. Die Infektion war auch unter den in Berührung gekommenen Mitgliedern der Haushalte ausgedehnt; 7 unter den 10 Geschwistern und 10 unter den 47 Erwachsenen waren viruspositiv. 85 % der Virusträger schieden viruspositive Stühle noch 4–5 Wochen nach dem ersten Auftreten der paralytischen Fälle aus und 25 % noch nach 7–9 Wochen. In der anderen Anstalt, einem vereinigten Kindergarten und Waisenhaus, war der paralytische Anzeigefall einen Monat früher aufgetreten und war von einem Fall aseptischer Meningitis, gerade bevor diese Untersuchung unternommen wurde, gefolgt. Man fand, dass 32 unter den 59 Kindern und 2 Mitglieder des Personals von 34 Erwachsenen Polioviren vom Typus 3 ausschieden. In diesem Falle wiesen 50 % der Virusausscheider poliovirusposítive Stuhlpräparate 6–7 Wochen nach dem Auftreten des paralytischen Anzeigefalles auf und 7 % noch nach 10–11 Wochen. Infektionen mit anderen Keimen wurden auch unter den beobachteten Kindern entdeckt. Bakterielle Krankheitskeime waren in beiden Ausbrüchen sehr allgemein und Adenoviren vom Typus 1, 2, 3 oder 5 wurden bei einer oder mehreren Gelegenheiten bei 15 Kindern, die zur zweiten Ausbruchgruppe gehörten, isoliert. Die zahlreichen Episoden von geringfügigen Krankheiten, denen wir bei den beobachteten Personen begegneten, konnten nicht definitiv irgendeinem unter den vorgefundenen Krankheitskeimen zur Last gelegt werden.

Infecciones con poliovirus tipos 2 y 3 en casas de asistencia infantil y un asilo de huérfanos.

En el otoño de 1955, cuando la incidencia poliomielítica era poco elevada en Estocolmo, se estudiaron dos brotes epidémicos de infecciones poliovíricas institucionales. En una casa de asistencia infantil diurna, en que se habían presentado dos casos paralíticos una y dos semanas anteriormente, 31 de los 33 niños y 2 de los 5 miembros del personal, excretaron poliovirus tipo 2. La infección también se había propagado entre los contactos domésticos, resultando 7 de los 10 descendientes directos y 10 de los 47 adultos viruspositivos. Ochenta y cinco por ciento de los excretantes de virus produjeron muestras fecales positivas ulteriores hasta 4–5 semanas después de la manifestación de los primeros casos paralíticos y 25 por ciento aún después de 7–9 semanas. En la otra institución, casa de asistencia infantil diurna y asilo de huérfanos combinados, el caso paralítico indicador se había manifestado un mes antes, siguiéndolo un caso de meningitis aséptica, justo antes de esta investigación. Se halló que treinta y dos de los 59 niños y 2 miembros del personal de 34 adultos, excretaban poliovirus tipo 3. En estos, 50 por ciento de los excretantes de virus, produjeron muestras positivas de poliovirus 6–7 semanas después de la manifestación del caso paralítico indicador y 7 por ciento aún después de 10–11 semanas. También fueron descubiertas infecciones debidas a otros agentes, entre los niños examinados. Las bacterias patógenas fueron por lo tanto comunes en ambos brotes y en una o varias ocasiones se recuperaron adenovirus tipos 1, 2, 3 ó 5, de 15 niños pertenecientes al segundo brote. Los numerosos episodios de enfermedad menor encontrados entre las personas examinadas, no pudieron correlacionarse difinitivamente con ninguna de las formas patógenas encontradas.

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Pertussis Complications and Mortality during the Period 1934 to 1953

by H. JERNELIUS

Of late the impression has prevailed—at least in Stockholm—that whooping-cough has changed its character, inasmuch as the course of illness has become milder. To collect more detailed information on this point and to study whether the introduction of sulphonamides and antibiotics has led to a decrease of complications and mortality, we have prepared a survey of 1131 cases during 4 two-year periods admitted to the Hospital for Contagious Diseases in Stockholm. For the first two years 1934 and 1935 were selected, to obtain a material preceding the introduction of sulphonamides. The remaining two-year periods then follow upon one another at six-year intervals, viz. 1940–41, 1946–47, and 1952–53. These periods coincide roughly with important changes in the treatment of complications and the respective adoptions of sulphonamides, penicillin, and broad-spectrum antibiotics.

Age Distribution and Indications for Admission

The age distribution within the entire series, 1131 cases, is given in Table 1. Infants constitute only 23 % of the entire series. This is due to one-half of the total of cases having been admitted on social indications. The infants are rather evenly distributed among the various age groups, the group 3–5 months being somewhat larger relatively.

As will be seen, the age distribution among the 4 two-year groups is about the same (Table 2). Possibly the group 3–5 months has somewhat increased at the expense of the group 6–11 months.

The totals of admissions for separate years are presented in Table 3. Approximately one-half of the admissions were due to social indications. Social indication for admission was considered to prevail if treatment at home was impossible, e.g. owing to the mother being employed, and if the case was uncomplicated. Also epidemiological indications for admission

TABLE 1

Age distribution within the entire series.

Age	Number	%
< 1 year	259	22.8
1– 2 years	418	37.0
3– 4 years	266	23.5
5–14 years	176	15.6
> 15 years	12	1.1
Total	1131	100.0
0– 2 months	56	21.6
3– 5 months	78	30.1
6–11 months	125	48.3

TABLE 2

Age distribution among the two-year periods.

Age	1934–35 %	1940–41 %	1946–47 %	1952–53 %
< 1 year	19.7	24.2	19.3	26.7
1–2 years	36.6	35.3	44.8	31.9
3–4 years	25.5	22.1	22.3	24.4
> 5 years	18.2	17.1	11.9	16.0
Number of cases	208	240	301	382
0– 2 months	17.1	27.6	18.9	21.6
3– 5 months	24.4	22.4	31.1	36.3
6–11 months	58.5	50.0	50.0	42.1

were counted as social ones; for example, when a patient was admitted in order to protect infants living in the house.

The totals of admissions show a stable increase from 208 in 1934–35 to 382 in 1952–53, concurrent with the increase in hospital beds and personnel. The rate of admission on social indication rose from 35% in 1934–35 to 52% in 1940–41; in 1946–47 it was 59%, and in 1952–53, 50%.

Complications

The incidence rates of various complications in the entire series and separate year groups respectively are given in Table 3. No attempt was

TABLE 3

Rate of complications.

Complications	Entire series Number	Entire series %	1934–35 %	1940–41 %	1946–47 %	1952–53 %
Bronchitis	237	20.8	10.6	22.1	22.3	24.8
Bronchopneumonia	153	13.5	15.8	20.0	13.3	8.4
Acute otitis media	55	4.9	10.1	5.4	2.7	3.4
Atelectasis pulm.	30	2.7	0.5	0.4	2.3	5.5
Hemolytic streptococcal infections (except scarlet fever)	23	2.0	2.9	1.3	0.7	3.1
Scarlet fever	20	1.8	3.8	1.3	1.3	1.3
Capillary bronchitis	13	1.2	1.4	1.7	1.0	0.8
Encephalitis	8	0.7	1.0	0.4	1.3	0.3
Mastoiditis	6	0.5	1.9	0.8	—	—
Myocarditis	2	0.2				
Acute nephritis	2	0.2				
Rectal prolapse	2	0.2				
Herniae	2	0.2				

made to segregate possible nosocomial infections, but all complications were included regardless of when they occurred. Concerning scarlet fever, however, it should be pointed out that there was no instance of nosocomial infection. The figure for the atelectasis rate in the entire material is certainly too low, since prior to 1946 pulmonary radiograms had been taken in but occasional instances, this being made a routine procedure for all cases not until 1952. Here the figure for 1952–53, viz. 5.5%, is in closer agreement with factual conditions.

When we consider the evidence for separate years, we find in the table that the pneumonia rate increased somewhat from 1934–35 on to 1940–41 and subsequently by degrees receded to about one-half. The differences are statistically highly significant. That the decrease did not occur until 1940–41 may be due to the cases being more carefully isolated after that period, for from the beginning of 1946 all cases of pertussis were collected in a special isolation ward. Likewise, the bronchitis rate rose up till 1940–41, but afterwards remained stable. Otitis decreased appreciably, mastoiditis has disappeared, as was to be expected. Atelectasis has already been discussed. Haemolytic streptococcal infection and scarlet fever appear to be as frequent now as formerly. Cases of capillary bronchitis and encephalitis are so rare that no definite statement can be made; a tendency towards decrease seems most probable.

The decrease of the pneumonia rate is most striking in the infants. Together with the cases of capillary bronchitis the pneumonia cases decreased from 24% in 1946–47 to 6% in 1952–53.

The marked drop in the pneumonia rate from 1946 to 1952 is indeed remarkable. It is reasonable to suppose that the antibiotics have played a significant part in this respect. They are rather liberally used in the management of mild complications such as bronchitis, rhinopharyngitis, etc., and probably the development of bronchopneumonia is to some extent prevented by this. However, short-term treatment of uncomplicated whooping-cough with chloramphenicol or tetracyclines cannot be expected to preclude pulmonary complications. There is no reliable basis for assessing whether, in addition, the disease as such might have become less severe. We have ascertained how many cases received antibiotic treatment in the hospital in 1952–53 and found fairly high figures. Among the 382 cases 36% had been treated with chloramphenicol or terramycin, and 31% with penicillin or sulphonamides. None of the patients had been vaccinated against pertussis.

Period of Hospitalization

On an average, the period of hospitalization for the cases admitted on social indication in the course of the years remained rather stable at about 5 weeks, viz. owing to the fact that these patients as a rule could not be discharged until they were non-infective. As to those admitted for purely medical reasons, the average stay in hospital dropped from roughly 4 weeks to 3 weeks. The difference is statistically significant. The decrease in the period of hospitalization probably results from a more effective treatment of complications.

Mortality

Pertussis mortality shows a gratifying decrease from 7 cases (3.4%) in 1934–35 to 5 (2.1%) in 1940–41, in 1946–47 it was 4 (1.3%), and in 1952–53 there were no fatalities. From 1947 onwards until the present time barely 2 fatalities occurred in pertussis at the Stockholm Hospital for Contagious Diseases, both in 1950. This decreasing mortality rate might be explained partly by improved general management, and partly by a more efficient treatment of pulmonary complications. Certainly, not only the administration of antibiotics but treatment of infants by means of the oxygen tent, more careful supervision, etc., have played an important part. The neg-

TABLE 4

Mortality in per cent in different age-groups of the material from the Stockholm Hospital for Contagious Diseases.

Age	1934–35	1940–41	1946–47	1952–53	Total
0– 2 months	14.3	18.8	36.4	—	14.3
3– 5 months	10.0	7.7	—	—	2.6
6–11 months	4.2	—	—	—	0.8
1–2 years	5.3	1.2	—	—	1.2
3–4 years	—	—	—	—	—
>5 years	—	—	—	—	—

ligible specific action of broad-spectrum antibiotics upon whooping-cough can hardly be credited with more than a very slight, if any, effect on mortality (5, 6). There is no doubt but that also increased natural resistance of the subjects, due to a higher standard of living with improving nutritional status, has been helpful.

For the sake of completeness, in addition we have considered the cases of pertussis treated in all the pediatric hospitals of Stockholm. In the 4 two-year periods there were only 123 cases treated in these hospitals. Two fatalities had been recorded.

As regards the mortality in different age-groups, it stands to reason that the fatality risk is highest for infants under the age of 3 months (Table 4). In the total material the mortality rate in this group is 12 times that of the children of between 1 and 3 years. In 1946–47 all fatalities occurred in the lowest age-group, and in 1952–53 there were no deaths.

In most instances, a pulmonary complication would seem to have been the cause of death: 5 patients died of capillary bronchitis, 6 of bronchopneumonia, 3 of encephalitis in conjunction with pneumonia or capillary bronchitis, and lastly, 2 uncomplicated cases terminated fatally. In the total 8 cases with encephalitis there were 3 fatalities.

To cover the broader aspect of mortality, we include the rates for the whole of Sweden during the past 30 years (Table 5). The death-rate shows a fairly steady decrease during the entire period, which suggests that in the first place general factors, such as a higher standard of living, better information, etc., have been instrumental. From the five-year period, 1931–35, to 1936–40 this decrease is accelerated; the infant mortality drops to one-half, and in older children to less than one-third. This coincides with the introduction of sulphonamide treatment, but also with the institution of

TABLE 5

Pertussis mortality in the whole Sweden 1921–53.

Year	Infant mortality		Mortality 1–4 years	
	No./year	‰	No./year	‰
1921–25	310	2.70	161	0.35
1926–30	177	1.82	93	0.24
1931–35	102	1.17	50	0.14
1936–40	56	0.60	15	0.04
1941–45	56	0.46	16	0.04
1946–50	26	0.21	7	0.01
1951–53	9	0.08	5	0.01

the National Preventive Infant Service. During the next five years there is a period of stagnation: here the influence of the war crisis should be suspected. After 1945 there is another sharp drop in mortality, possibly connected with the introduction of penicillin and other antibiotics. This last period includes only three years, the figures since 1953 not having been published. A continued decrease in mortality may be expected, owing in particular to further expansion of new wards for infectious diseases. At present the major proportion of fatalities occur in rural areas.

Table 6 shows the infant mortality of pertussis during recent years in Sweden and some other countries. To save space not all countries are represented for which statistics were available, but everywhere except in the U.S.A. the mortality rate is several times higher than in Sweden. This is true also of the Scandinavian countries. This observation is not easily explained. There is nothing to suggest that in Sweden the pertussis bacteria

TABLE 6

Infant mortality of pertussis in Sweden and some other countries 1951–53.

Country	‰
Sweden	0.08
U.S.A.	0.10
Switzerland	0.25
England and Wales	0.27
Netherlands	0.29
Denmark	0.37
France	0.39

belong to a less virulent type. Triple vaccination can hardly be credited, as it was rather sparingly used in Sweden during the years in question. The high economic and social standard and, above all, the energetic preventive infant service with practically 100 % checking of infant health would seem to be of paramount importance for the low mortality in Sweden.

Whooping-cough is about to lose its position as a very serious children's disease, and, provided that the patients are adequately cared for and efficiently treated, scarcely any mortality at all needs to be taken into account. Certain complications in those admitted to hospital, especially pneumonia, have apparently decreased in incidence during recent years. However, the disease still brings great distress to the children and their attendants as long as we lack an effective causal treatment.

Summary

The writer has surveyed 1131 cases of pertussis admitted to the Stockholm Hospital for Contagious Diseases during the years 1934–35, 1940–41, 1946–47 and 1952–53. The age distribution was practically identical among the 4 two-year groups, about 20 % of the patients being infants. Roughly one-half of all cases had been admitted on social indications. The incidence rates of complications were compared, and it was found that bronchopneumonia had decreased from 15 % in 1934–35 to 8 % in 1952–53. The mortality rate in 1934–35 was 3.4 %, but subsequently it dropped gradually to nil during the years 1952–53. After the year 1946, only 2 fatalities occurred at the hospital. Data are presented concerning the development of pertussis mortality in the whole of Sweden; during the years 1951–1953, the infant mortality had reached the exceedingly low rate of 0.08 per mille. In the writer's opinion this is due to the contributory benefit derived from general social factors such as the higher standard of living and the preventive infant service and, in recent years, to the effective treatment of pulmonary complications with antibiotics. At present Sweden has the world's lowest infant mortality of pertussis.

Complications et taux de mortalité de la coqueluche au cours de la période de 1934 à 1953.

L'auteur passe en revue 1131 cas de coqueluche qui furent admis à l'Hôpital pour Maladies Contagieuses de Stockholm au cours des années 1934–35, 1940–41, 1946–47 et 1952–53. La répartition par catégories d'âge était à peu près la même pour chacune de ces périodes de deux ans et l'on retrouvait chaque fois environ 20 % de bébés parmi les malades. La moitié environ de l'ensemble des malades avaient été pris en charge par l'hôpital à la suite de rapports des services d'Assistance Sociale. L'auteur s'est livré à une étude comparative de l'incidence des complications survenues au cours de ces différentes périodes et il a constaté que l'incidence de la bronchopneumonie qui était de 15 % en 1934–35 était tombée à 8 % en 1952–53. De même, le taux de mortalité qui était de 3,4 % en 1934–35, avait diminué par la suite pour tomber à zéro en 1952–53. Depuis 1946, deux cas mortels seulement ont été enregistrés à l'hôpital. L'auteur donne alors des renseignements sur l'évolution du taux de la mortalité due à la coqueluche dans toute la Suède; pour la période de 1951 à 1953, la mortalité chez les

nourrissons est descendue au taux extrêmement réduit de 0,08 pour mille. L'auteur pense que cette évolution favorable est le résultat de l'amélioration générale des conditions sociales et qu'elle est notamment due à l'élévation du standard de vie, à l'action du Service d'Hygiène Infantile et, dans les dernières années, à l'efficacité du traitement des complications pulmonaires par les antibiotiques. A l'heure actuelle, la Suède est de tous les pays du monde, celui où la mortalité infantile due à la coqueluche est la plus faible.

Keuchhusten-Komplikationen und Sterblichkeit in der Zeit von 1934 bis 1953.

Der Verfasser hat eine Übersicht von 1131 Fällen von Keuchhusten, die in den Jahren 1934–35, 1940–41, 1946–47 und 1952–53 in das Infektionskrankenhaus in Stockholm zugelassen worden waren, angestellt. Die Altersverteilung war in den 4 Zweijahrgruppen für praktische Zwecke identisch und 20 % der Kranken waren Kleinkinder. Ungefähr 50 % aller Fälle wurden auf Grund einer sozialen Indikation aufgenommen. Das Auftreten von Komplikationen wurde verglichen und es wurde festgestellt, dass der Bronchopneumoniesatz von 15 % in 1934–35 auf 8 % in 1952–53 herabgefallen war. Der Sterblichkeitssatz betrug 3,4 % in den Jahren 1934–35 und fiel in den darauffolgenden Jahren allmählich bis auf 0 % in 1952–53 herab. Nach dem Jahre 1946 kamen nur 2 Todesfälle in dem Krankenhaus vor. Angaben über die Entfaltung der Pertussis-Mortalität in ganz Schweden werden angeführt; in den Jahren 1951–53 hatte die Kleinkindersterblichkeit den ausserordentlich niedrigen Grad von 0,08 per Tausend erreicht. Dies ist nach Ansicht des Verfassers eine Folge günstig einwirkender allgemeiner sozialer Faktoren, wie höherer Lebensstandard und Kindergesundheitspflege, sowie in den letzteren Jahren ausserdem durch wirksame Behandlung von Lungenkomplikationen mit Antibioticis bedingt. Gegenwärtig weist Schweden den niedrigsten Kleinkindersterblichkeitssatz für Keuchhusten in der ganzen Welt auf.

Tos ferina: complicaciones y mortalidad entre 1934 y 1953.

Durante los años de 1934–35, 1940–41, 1946–47 y 1952–53, el autor ha estudiado 1131 casos de tos ferina, ingresados en el Hospital de enfermedades contagiosas de Estocolmo. En cada uno de estos 4 períodos bienales, correspondieron en forma idéntica las edades de los pacientes, debiendo atribuirse un 20 % de los casos afectados a niños lactantes. En conjunto, la mitad de todos los casos fueron ingresados por indicaciones de orden social. Se compararon los promedios de incidencia y se halló que había disminuído la bronconeumonia de un 15 % en 1934–35 a un 8 % en 1952–53. El promedio de la mortalidad fué de un 3,4 % en 1934–35, bajando gradualmente al 0 % durante los años 1952–53. Después del año 1946, solo se produjeron dos casos mortales en el Hospital. Se presentan datos acerca del desarrollo de la mortalidad debida a la tos ferina en todo el país de Suecia; durante los años 1951–53, la mortalidad de los niños lactantes había alcanzado el nivel extremadamente inferior del 0,08 por mil. El autor opina que ello se debe a normas sociales más elevadas y también al Servicio de Sanidad Infantil, así como, en años recientes, al tratamiento efectivo de las complicaciones pulmonares con antibióticos. Actualmente Suecia detiene la más baja cifra mundial de mortalidad infantil consecuencia de tos ferina.

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From the Pediatric Clinic of the University of Amsterdam (Head: Prof. Dr. S. van Creveld)

Complications of Intracutaneous BCG Vaccination in Newborn Infants

A Survey 3 1/2 Years After the Vaccinations[1]

by MARIE R. H. STOPPELMAN and E. F. DRION[2]

In the period from March 1st, 1951, to February 15th, 1952, all the infants born at the Lying-in Hospital of the University of Amsterdam were vaccinated intracutaneously with BCG vaccine. The vaccine was prepared by the Dutch State Serological Institute from a Danish BCG strain. Vaccinations were done once a week by a single pediatrician. One-tenth ml of the vaccine, containing 0.33 mg of bacteria per ml, was injected intradermally in both arms (Group 1).

The infants were examined three months after the vaccination. When the occurrence of many cases of regional lymphadenitis with suppuration was noted the dosage was reduced to 0.05 ml on each side (Group 2). This reduction was instituted in August 1951. Since the number of cases with regional lymphadenitis remained rather high, though less than in the first group of infants, at the end of November 1951 it was decided to reduce the dosage once more. After December 1st, 1951, the infants received two intracutaneous injections of 0.03 ml of BCG vaccine (Group 3).

This routine vaccination ended on February 15th, 1952. Since in Holland many cases of lymphadenitis with suppuration were noted not only in the infants inoculated intradermally but also in those inoculated orally, the Public Health Authorities decided to discontinue the mass vaccination. Since February 1952 vaccination has been limited to infants exposed to infection.

Most of the infants were examined at the Out-patients Department of the Pediatric Clinic of the University of Amsterdam three months after the

[1] This investigation was financially supported by the Netherlands Organization for Applied Scientific Research (T.N.O.).

[2] The Statistic Department of the Central National Council for Applied Scientific Research in the Netherlands T.N.O.

TABLE 1

Number of children examined 3 1/2 years after the BCG vaccination.

Group	Number of inoculated children	Number of children not re-examined	Number of deceased	Number of children re-examined 3 1/2 years after vaccination
1	809	126	9	674 (83.3 %)
2	681	98	6	577 (84.7 %)
3	459	98	4	357 (77.8 %)
Total	1949	322	19	1608 (82.5 %)

BCG immunization. The majority of the infants who were not seen at the clinic were visited and examined at home at a later date, varying from 11 to 16 months after vaccination. In this way it was possible to examine 92.5% of all the vaccinated infants. The tuberculin skin test (in a dilution of 1:1000) was positive in more than 99% of the infants of the first two groups and in 98% of those in the third group, who had been injected intradermally with 0.03 ml of the BCG vaccine on each side.

The children vaccinated with BCG of the three above-mentioned groups were re-examined 3½ years after the immunization. Most of the children were examined at the Out-patients Department; the others were seen at home. It was not possible to re-examine all the vaccinated children. Some families had moved away, a fair number had emigrated, some of the parents refused to cooperate and some of the children had died.

In the first table the number of children re-examined 3½ years after the administration of BCG vaccine is given for each group. Of the 1949 children vaccinated, 1608 were re-examined and tested for tuberculin sensitivity. During the first months of this examination the Mantoux test was carried out in a dilution of 1:1000. Where possible the negative reactors were retested with tuberculin diluted 1:100. When it was found that many of the children of Group 2 reacted negatively to the intracutaneous injection of 0.1 ml of 1:1000 diluted tuberculin, it was decided to use only the 1:100 dilution of tuberculin.

Although non-specific skin reactions with rather concentrated tuberculin solutions have been seen, these false, positive reactions have not been observed in children under 4 years of age. Since the positive reaction following BCG vaccination is less marked than after infection with virulent tubercle bacteria it has even been recommended that 1:100 diluted tuberculin be used in testing BCG vaccinated persons. Only the tests which showed an infiltration with a diameter of at least 5 mm were noted as positive. The

TABLE 2

Tuberculin test 3 1/2 years after BCG vaccination.

Group	Total number of children	Intracutaneous tuberculin test					Percutaneous tub. test	
		1:1000 pos. No.	1:1000[a] neg. No.	1:100 pos. No.	1:100[b] neg. No.	%	pos. No.	neg. No.
1	674	461	4	180	10	1.5	19	0
2	577	19	7	469	72	12.5	10	0
3	357			328	15	4.2	13	1

[a] Test in dilution 1 : 100 not done.
[b] Diameter of induration less than 5 mm.

specificity of the skin test will also be discussed in connection with the results of the statistical analysis.

A few children whose parents objected to the intradermal injection were tested by the percutaneous method.

The results of the tuberculin sensitivity tests in the three groups are shown in Table 2.

The data in Table 2 show that only one out of 42 children had a negative percutaneous skin test. The parents of the children who had had suppurated lymph glands objected to the intradermal injection; the sensitivity to tuberculin in the children who had suffered from these complications was more marked than in the other children.

No difference in the results of the skin tests between the group of known contacts and the group who had not been exposed to known sources of infection was seen. As appears in Table 2, contrary to expectation the percentage of negative Mantoux tests in a dilution of 1 : 100 was significantly higher in Group 2 than in Group 3. The children of Group 3 had received a smaller dose of BCG vaccine than the children of Group 2. For this reason it was decided to determine the percentage of negative tuberculin tests and the percentage of suppuration of regional lymph glands separately for each small group of children vaccinated on the same date.

Statistical Treatment of the Data[1]

On each of the inoculation dates the numbers of negative reactions in Group 1 and 3 were very small. With such small numbers an exact statistical test is not very well possible; a rough comparison with the Poisson distribu-

[1] By the Statistics Department of the Central National Council for Applied Scientific Research in the Netherlands T.N.O.

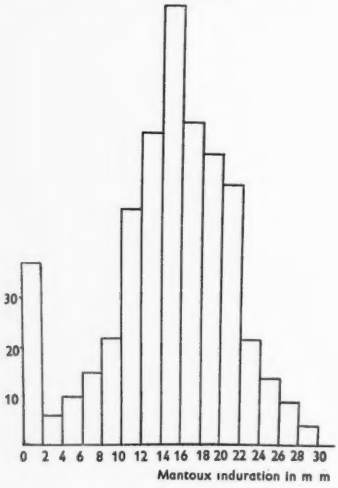

Fig. 1.

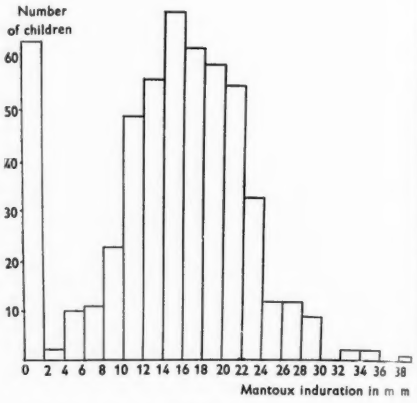

Fig. 2.

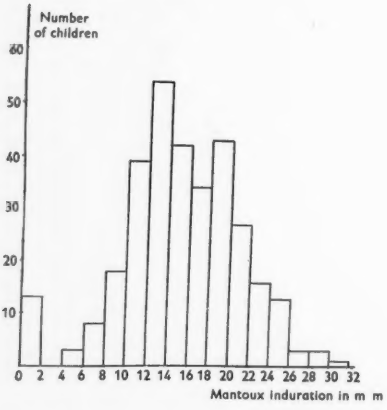

Fig. 3.

tion shows that there is no reason to suppose that the fluctuations in the number of negatives was due to anything but chance. In Group 2, however, there are two dates, one at the beginning of August and one at the end of October 1951, on which a relatively large percentage of negative results were found, i.e., 76.5% and 32.1% respectively. These two percentages differ significantly from the frequency of the negative results in this group on the other dates.

In Group 1 no important difference between the frequency distributions of the non-zero Mantoux indurations on different dates was to be found;

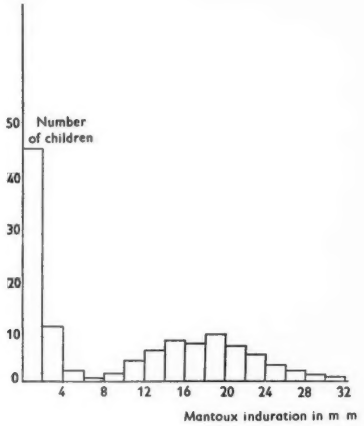

Fig. 4.

in Group 3 the differences between the frequency distributions on different dates was not larger than in Group 1, therefore no test was applied.

In Group 2, omitting the two dates with a significantly higher percentage, the percentage of negative Mantoux reactions is 6.9%, which differs little from the percentage found in Group 3. The data on suppuration of the lymph glands shows that the frequency of this complication also varies between children inoculated on different dates. This will be treated in the paragraph on complications.

In the histograms (Figs. 1, 2 and 3) the frequency distributions of the diameter of the Mantoux induration in each of the three groups is shown; the observations have been grouped in classes of 2 mm. The practically symmetrical form of the histograms is an indication that in this group of children, inoculated three years previously, indurations with a smaller diameter (1 mm to 5 mm) are to be considered as specific reactions. This is confirmed by the cumulative frequency distribution of all non-zero indurations; on normal-probability paper the graph of this distribution shows a straight line. Not even the smallest indurations deviate from this line. Although this linearity does not prove that the border between positive and negative is at about 1 mm, it is certainly an indication for this position of the border.

For comparison a histogram of the frequency distribution of the diameter of Mantoux indurations (tuberculin 1:1000) of non-inoculated adults is given, copied from an article by Palmer; from this histogram (Fig. 4) it may be concluded that in this case the small indurations were not specific.

The median of the non-zero indurations is 15.5 mm; 50% of the children

Fig. 5.

with a positive reaction therefore had an induration of 15.5 mm or more. The mean of the non-zero indurations is 15.7 mm; since the frequency curve is almost symmetrical this is about equal to the median induration.

Complications

The complications seen at the first examination, while the children were in their infancy, were:

(*a*) enlargement of regional lymph glands;
(*b*) suppuration of regional lymph glands;
(*c*) tuberculid eruptions on the skin;
(*d*) conjunctivitis phlyctaenulosa.

Complications (*c*) and (*d*) were seen in only a few infants and disappeared after two or three months.

(*a*) At the final examination, 3½ years after the inoculation with BCG vaccine, 6 children showed enlarged regional axillar, supraclavicular or infraclavicular lymph glands (see Fig. 5). Four of these six had already had suppurated lymph glands in infancy. Five of them belonged to Group 1 and one to Group 2.

TABLE 3

Group	Number of children examined	Children with suppurated lymph glands		Lapse of time between inoculation and suppuration		
		No.	%	0–6 mo.	6–10 mo.	> 10 mo.
1	674	179	26.6	99	36	44
2	577	41	7.1	15	12	14
3	357	11	3.1	2	3	6

Fig. 6.

(*b*) Table 3 shows the number and percentage of children in each group who had had suppuration of regional lymph glands. The lapse of time between the BCG vaccination and the moment when suppuration was first noted is mentioned in the same table. In a great number of cases suppuration occurred ten months and more after the inoculation with BCG vaccine. Thus an examination of infants three and six months after vaccination does not provide reliable information about the frequency of complications. Six children from Group 1 and one child from Group 2 showed suppurated regional lymph glands $3\frac{1}{2}$ years after vaccination (Fig. 6). In one of the children enlargement of the lymph gland that later suppurated was first noted at the age of three and in another at the age of two. In five of the seven children pus was aspirated. (Bacteriological examinations were done at the Bacteriological Department of the Municipal Health Organization of Amsterdam (chief bacteriologist, G. J. Schaap) and at the bacteriological laboratory of "het Binnen Gasthuis" (bacteriologist, Dr. N. Lubsen).)

At the first examination three years ago acid-fast bacteria were isolated in 19 instances. The results of the cultures in the last five cases were negative.

In a number of children calcified axillary lymph glands were seen at the roentgenological examination of the thorax (Fig. 7).

A statistical analysis of the frequency of suppuration of lymph glands after BCG inoculation gives the following results:

In Groups 2 and 3 suppuration of lymph glands was a complication of such relative infrequency that the normal statistical tests could not be used. Since, however, in Groups 2 and 3 the distribution of the numbers of children with suppuration of the glands at different dates was indistinguishable from a Poisson distribution there is no reason to suppose that the probability of this complication at different dates was otherwise.

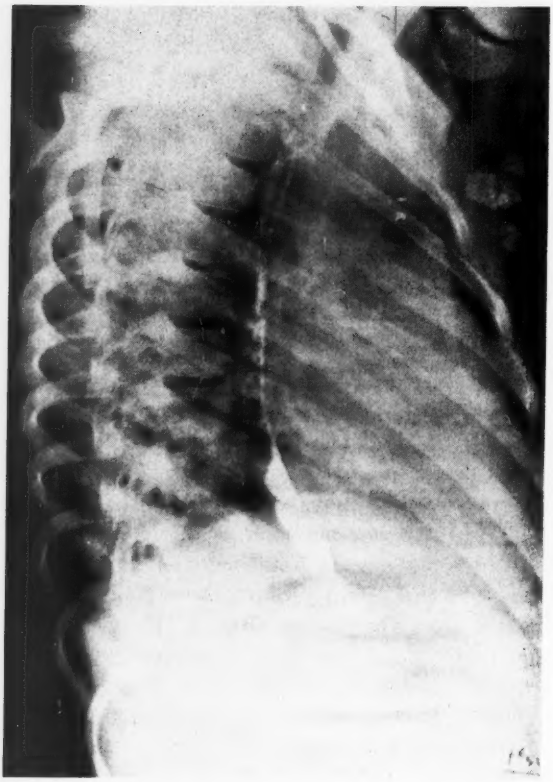

Fig. 7.

In Group 1 suppuration of the lymph glands was rather frequent. For each date the number of children with this complication was calculated according to the hypothesis that its occurrence was probably the same for each date, i.e., 27%. From the differences between the observed and the calculated number of children with suppuration of the glands the statistic χ^2 was drawn. The value of χ^2 is 44.8; with 19 degrees of freedom, this would correspond to a significance level of less than 0.001, which proves that in Group 1 the probability of suppuration of the lymph glands was different at different dates.

It appeared that both in the rate of occurrence of a negative Mantoux reaction and that of suppuration of the lymph glands there were differences between children vaccinated at different dates. The cause of these statistically significant differences could not be established.

No cases of tuberculosis were found among the 1608 children.[1] Over a period of 3½ years nineteen children had died. In fifteen cases the cause of death is known and no correlation was found between the death and the BCG vaccination. The other four children had died suddenly and no autopsy was performed.

Comment

Re-examination of 1608 of the 1949 children who had been inoculated intradermally with BCG vaccine in the neonatal period showed that:

(1) Three and a half years after the vaccination the percentage of tuberculin positive reactors in the three groups varied between 98 and 87.5.

No difference in tuberculin sensitivity was observed between the children who had been in contact with cases of tuberculosis and those without known contact.

The percentage of the positive reactions due to infection with tubercle bacteria cannot be determined.

(2) The percentage of children with suppuration of regional lymph glands was high. In Group 3, comprising the children who had received two injections of 0.03 ml of the BCG vaccine, suppuration was noted in 3%.

Some children showed enlargement of regional lymph glands as late as 3½ years after vaccination and at that period seven children had suppurated lymph glands. In a large proportion of the cases it proved that suppuration of the lymph glands had occurred ten months or longer after the inoculation.

(3) Statistically significant differences between the small groups of children, classed according to the date of vaccination, were found not only in the rate of complications but also in the percentage of tuberculin negative reactions. The factor or factors which caused these discrepancies are unknown. In the "Centre International de l'Enfance" at Paris differences in potency between several batches of BCG vaccine prepared on different days by the same laboratory have been demonstrated.

4. During the period of 3½ years nineteen of the children inoculated with BCG vaccine had died. In fifteen cases the cause of death is known and no correlation was found between the fatal illness and the inoculation. In the other four cases of sudden death was reported.

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We are indebted to Drs. C. Coster, P. H. Bloch, L. A. J. M. van Eck, J. J. Hoogervorst, J. C. Huizinga, G. Mak, A. F. Meyer, W. H. J. Oderwald, R. van Oppen and H. Posthumus for their valuable help.

[1] From 1951 to 1953 the Clinic of the Association for the Prevention of Tuberculosis at Amsterdam reported 3, 5 and 4 cases of tuberculosis per year respectively among the infants in Amsterdam. The number of new cases of tuberculosis among the children of 1–4 years of age was 67, 41 and 30 annually during the same period.

Summary

A large number of children who had been vaccinated intracutaneously with BCG vaccine in the neonatal period were re-examined 3½ years after vaccination. This study comprises three groups of children:

Group 1, who received 2 injections of 0.1 ml of BCG vaccine; Group 2, who received 2 injections of 0.05 ml; and Group 3, who received 2 injections of 0.03 ml. Of 1949 children vaccinated 3½ years previously, 1608 could be rechecked. The Mantoux test in a dilution of 1 : 100 was positive in 87.5 to 98 per cent of all cases.

Suppuration of regional lymph glands occurred in 26.6 per cent of the children of Group 1, in 7.1 per cent of those in Group 2, and in 3.1 per cent of those of Group 3. In many cases suppuration of one or more regional lymph glands began 10 months or longer after BCG vaccination. Six children showed enlargement of regional lymph glands, and seven children had suppurated regional glands three and a half years after vaccination with BCG. In five children pus was aspirated and examined bacteriologically; no acid-fast bacteria were isolated by the bacteriologist. The percentages of negative skin tests and complications showed statistically significant differences in the small groups of children arranged according to date of vaccination.

Complications de la vaccination par le B.C.G. par voie intradermique chez les nouveau-nés. Résultats d'un contrôle effectué trois ans et demi après la vaccination.

Cette étude a porté sur trois groupes d'enfants : le groupe 1 se composait d'enfants qui avaient reçu deux injections de 0,1 cm³ de vaccin B.C.G.; les enfants du groupe 2 avaient reçu deux injections de 0,05 cm³ et ceux du groupe 3, deux injections de 0,03 cm³. Sur 1949 enfants qui avaient été vaccinés trois ans et demi auparavant, 1608 purent être contrôlés à nouveau. Le test de Mantoux à la dilution de 1:100 fut positif dans 87,5 à 98 % des cas. Des suppurations de ganglions lymphatiques régionaux furent observées chez 26,6 % des enfants du groupe 1, chez 7,1 % des enfants du groupe 2 et chez 3,1 % des enfants du groupe 3. Dans beaucoup de cas, les suppurations d'un ou plusieurs ganglions lymphatiques régionaux débutèrent au bout de 10 mois ou davantage après la vaccination B.C.G. Trois ans et demi après la vaccination par le B.C.G., six enfants présentaient une hypertrophie et sept autres, des suppurations de ganglions lymphatiques régionaux. Une ponction fut pratiquée chez cinq enfants et les échantillons prélevés furent soumis à un examen bactériologique; aucune bactérie acidorésistante ne fut isolée par le bactériologiste. Les pourcentages statistiques des cutiréactions positives et des complications observées dans les divers petits groupes d'enfants classés d'après les dates de vaccination, accusent des différences sensibles.

Komplikationen bei intrakutaner BCG-Impfung von Neugeborenen. Übersicht 3½ Jahre nach der Impfung.

Diese Studie umfasst drei Gruppen von Kindern: die 1. Gruppe, welche 2 Injektionen von je 0,1 ml BCG Vakzine erhielt, die 2. Gruppe, die 2 Injektionen von je 0,05 ml erhielt und die 3. Gruppe, die 2 Injektionen von je 0,03 ml erhielt. Von 1949 vor 3½ Jahren geimpften Kindern konnten 1608 wiederuntersucht werden. Die Mantoux-Probe bei einer 1:100 Verdünnung fiel bei 87,5–98 % aller Fälle positiv aus. Vereiterung der regionalen Lymphdrüsen kam bei 26,6 % der Kinder in der 1. Gruppe vor, bei 7,1 % der Kinder in der 2. Gruppe und bei 3,1 % der Kinder in der 3. Gruppe. I

vielen Fällen setzte die Vereiterung einer oder mehrerer regionalen Lymphdrüsen 10 Monate oder länger nach der BCG-Impfung ein. Sechs Kinder wiesen Vergrösserung der regionalen Lymphdrüsen und 7 Kinder vereiterte regionale Drüsen 3½ Jahre nach der BCG-Impfung auf. Bei 5 Kindern wurde der Eiter abgesaugt und bakteriologisch untersucht; keine säurefesten Bakterien wurden isoliert. Der Prozentsatz negativer Hautproben und von Komplikationen zeigte statistisch bedeutsame Unterschiede zwischen kleinen Gruppen von Kindern, die je nach dem Zeitpunkt der Impfung angeordnet worden waren.

Complicaciones de la vacuna B.C.G. intracutánea en los recién nacidos. Reconfrontación de los casos vacunados 3½ años después.

Este estudio comprende tres grupos de niños: Grupo 1, con 2 inyecciones de 0,1 ml de vacuna B.C.G.; Grupo 2, con 2 inyecciones de 0,05 ml y Grupo 3, con 2 inyecciones de 0,03 ml. De los 1949 niños vacunados tres años y medio antes, se reconfrontan 1608. Prueba de Mantoux en una dilución de 1 a 100, positiva en 87,5 a 98 por ciento de todos los casos. Supuración de las glándulas linfáticas regionales, en 26,6 por ciento de los niños en el Grupo 1; 7,1 por ciento, Grupo 2, y 3,1 por ciento Grupo 3. En muchos casos, supuración de una o más glándulas linfáticas regionales, a partir de los diez meses o más, después de practicada la vacuna B.C.G. Seis niños presentan amplificación de las glándulas linfáticas regionales, y siete niños supuración de las glándulas regionales, tres años y medio después de practicada la vacuna B.C.G. El pus de seis niños es aspirado y examinado bacteriológicamente; no han sido aisladas bacterias ácidoresistentes. El porcentaje de las pruebas cutáneas negativas y de las complicaciones presentan diferencias estadísticamente significativas en los pequeños grupos de niños dispuestos en orden de fechas de vacunación.

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Renal Hyperchloremic Acidosis

by I. OLOW and L. PAULSEN

Among the clientele in a pediatric ward, it is not very unusual to find vomiting children. Diagnostic problems are often involved with these cases, but the history, age and status of the child make it easy for the physician to find out the original cause. The group of children vomiting habitually and suffering from ruminatio, in the first place directs the attention to anatomical changes in the oesophagus or the stomach or to various factors concerning the milieu. These children are often regarded as "nervous children".

Research during the last few years, however, has shown that the last-mentioned group—which is troublesome and irritating both for the parents and the physician—includes children who may suffer from a serious disturbance. An early treatment of these disturbances may be of the greatest importance for the continued course of the disease.

In 1935 Lightwood (9) described a case of nephrocalcinosis infantum with acidosis in the blood and alkalosis in the urine. In 1939 Hartmann (7) reported one case of idiopathic renal acidosis with hyperelectrolytemia. Similar cases have been reported by, *inter alia*, Butler (3), Stapleton & Weston (12). Doxiadis (4) and Gabrielsen (6), and in adults by Albright & Greenspan (2) and Lundbæk (8). The symptoms of the disease, nowadays called after Lightwood, were described by him on the basis of 35 cases, published up to 1953, and are as follows:—

Onset before 18 months of age, anorexia, unprogressive weight, or loss of weight, vomiting, constipation and general hypotonia. In the blood there are increased total cations which do not correspond to desiccation, low HCO_3^- values, hyperchloremia, hypersodiemia, often normal potassium values, normal calcium and phosphorus values. Increased NPN was found in 50 per cent of the cases. The urine is neutral or gives a slight alkaline reaction and the specific gravity is low. In six cases Lightwood managed

to demonstrate calcium deposits in the kidneys, but points out that these deposits are of little importance for the diagnosis, as a lack of them does not exclude the diagnosis, and as calcium in the kidneys may be found in connection with other diseases as well.

During the last year a child has been treated at the Childrens' Hospital suffering from hyperelectrolytemia and azotemia with symptoms closely corresponding to the syndrome described by Lightwood.

Case History

Premature girl, born Nov. 7, 1954. Birth weight 1.500 g. During the neonatal period, the patient was cyanotic with apnoe on one occasion. At the age of one month her condition was impaired for some time with marked deep respiration. The blood showed low HCO_3^- values and increased total cations, but her condition improved after blood transfusion and supply of bicarbonate. In July 1955, the patient started vomiting in connection with meals and about one hour afterwards. The stools were of a marked hard consistency. Her weight on admission was 4.960 g at the age of 8 months. She was slender but, otherwise, bright and alert and psychically normal. During the first weeks she vomited about 100 g daily, was constipated and the increase of weight was slow.

X-ray examination of the *stomach* and *oesophagus* was normal. X-ray of the *skeleton* showed a normal quantity of ossification centers and no other skeletal changes. X-ray of the *kidneys* on several occasions showed no calcium deposits. The urine was slightly alkaline with traces of protein (½ ‰). Diuresis: 200–300 ml. Urine microscopy was normal. *Spec. weight of the urine* varied from 1.010–1.018. *Urea clearance* was 14.5 % of the normal, *endogenous creatinine clearance* 8.5 L/24 hrs. *Paper chromotography* of the urine showed normal content of amino acids. The electrolytes in the blood and urine of the patient are shown in Figs. 1 and 2. In Fig. 1 the high sodium, potassium and chloride values in the blood are noticed as well as the high NPN. Fig. 2 shows acidosis in the blood with the pH mainly on the acid side and reduced total-CO_2. Contrary to this the *urine gives an alkaline reaction* with comparatively great HCO_3^- secretion and slightly varying ammonia secretion. The serum protein, serum calcium, serum phosphorus and chloride and sodium secretion in the urine were normal. The potassium secretion was slightly reduced, and the calcium and phosphorus secretions were normal.

The observations were made during a period of three months partly with sodium citrate treatment, partly without. However, no noticeable difference was found between the blood and urine values during the two periods, although the sodium values in the blood seem to be higher during the treatment with citrate.

The diagnosis, Lightwood's syndrome was considered as probable, and the patient was treated from Nov. 1955 with sodium citrate per os in order to reduce the acidosis in the blood. The general condition of the patient during the hospitalization was comparatively satisfactory. The weight increased slowly, however; in Feb. 1956 she weighed 6.900 g and her height was 76 cm at the age of one year and 3 months. During June and July 1956 her general condition became impaired, the NPN increased (up to 200 mg %) and the vomiting increased. In Aug.–Sept. her condition improved with a decreasing NPN. A test of her psychical status at the age of one year and 6 months showed a decided under-development. Head size smaller than normal.

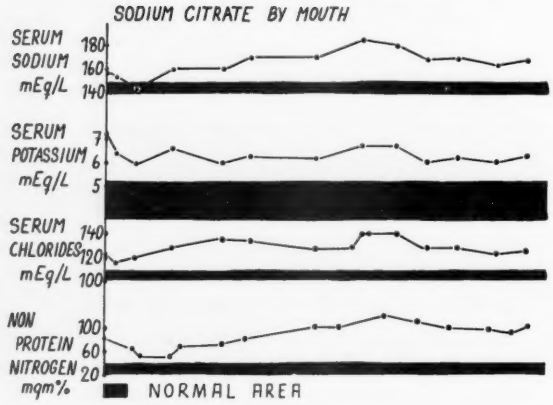

Fig. 1. Sodium, potassium and chlorides in serum and N.P.M. in blood during 3 months.

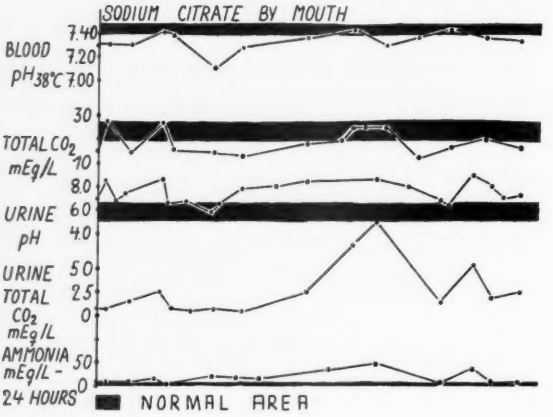

Fig. 2. Acid-base balance in blood, urine pH, urine total-CO_2 and ammonia excretion/24 hours during 3 months.

During the last six months her daily diet consisted of 700 g gruel, 200 g fruit soup and about 100 g milk, as well as 150 g stewed and mashed apples. She has not been able to receive more solid food. The content of sodium, potassium and chlorides of this diet almost corresponds to the secretion of these substances in the urine.

Discussion

Clinically the general symptoms in Lightwood's syndrome may occur also with other diseases, e.g. nutritional disturbances, pyloric stenosis, celiac disease, tuberculous meningitis and chronic intoxications.

D-vitamin resistant rachitis, Fanconi's syndrome, idiopathic hypercalcemia and other conditions which involve the kidneys may cause electrolytic disturbances resembling those found in Lightwood's syndrome. How-

ever, all these conditions also show other symptoms and findings which do not agree with Lightwood's syndrome.

As regards the *pathogenesis* of this syndrome, there are different opinions:

(1) *Albright et al.* (1) suggest the hypothesis that the kidneys may be unable to form ammonia. This, however, leads to a *loss of cations* but would not cause an *alkaline reaction in the urine*. In our case it has not been possible to demonstrate this inability.

(2) *Hartmann* (7) believes that primarily it is a matter of a loss of HCO_3^- via the urine and *Smith & Schreiner* (11) agree with Hartmann and in particular point out that during HCO_3^- therapy there is a secretion of HCO_3^- in the urine despite of the low plasma HCO_3^-. According to *Pitts et al.* (10) the renal treshold of HCO_3^- lies on 24 mekv/l (possibly slightly lower in children). At lower values, all the HCO_3^- is re-absorbed.

(3) According to the prevailing concept, especially advocated by *Fanconi* (5) the re-absorption of HCO_3^- occurs in the distal part of the tubules and according to investigations performed by *Pitts et al.* the enzyme, karbanhydrase takes an active part as this enzyme catalyses the process: $CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$. HCO_3^- is re-absorbed together with a sodium ion from Na_2HPO_4 which in turn takes up H^+, and is secreted in the urine as NaH_2PO_4. Another possibility is that H^+ is secreted with NH_3 as NH_4Cl. A dysfunction of this enzyme would thus cause inability to secrete H^+ ions and a loss of HCO_3^-, *but not cause hypersodiemia. Gabrielsen* (6) believes that such a dysfunction of the enzyme also would result in a reduced HCl-production in the stomach, but neither he nor we have managed to demonstrate this. However, it may be possible that a dysfunction could be localized to the kidneys only.

(4) According to the opinion of others as well as our own, one of the principal points in the picture of this disease is the inability of the kidney to acidify the urine even with an extra addition of acid. When charging the patient with 2 g NH_4Cl per os, we obtained a decrease in the blood pH (7.34→7.12) but not in the urine pH (Fig. 3). *Lundbaek* (8) considers this to be so typical for the disease that he has named it *anacidogenesis renalis.*

Besides this inability to secrete acid urine, our patient has a *hyperosmotic syndrome*, and obviously it is possible that this hyperosmotic condition may be due to an adrenal cortex damage, a central nervous dysfunction or a pure kidney damage. *Lightwood* in his cases could not demonstrate any signs of adrenal cortex damage and our patient does not show any clinical symptoms of this; the number of circulating eosinophil cells in the blood was normal and the content of 17-ketosteroids in the urine was also normal.

Our investigations do not support either the one or the other of these pathogenetic possibilities with certainty, but it is possible that in this case, besides a tubular damage there also is a *glomerular lesion*. The high NPN points to this, as well as the protein in the urine and the low creatinine clearance.

The electrolytic disturbances can be explained in different ways: a primary deficiency in the H^+ exchange or a primary deficiency in the HCO_3^- re-absorption or a *combination* of both these. The *high sodium* content in the blood may depend on a *primary increase in the chloride re-absorption.*

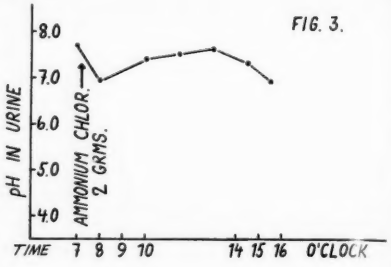

Fig. 3. pH in urine after charging with ammonium chloride.

As mentioned, we have treated the patient with sodium citrate hoping to increase the plasma HCO_3^-. At the same time the patient received extra sodium which theoretically ought to be incorrect. During this therapy no certain effect on the blood and urine chemistry could be demonstrated. Another therapeutic possibility was to remove sodium and chloride from the patient's diet with an ion exchanger, but has not been tried in this case.

The prognosis of this syndrome is considered to be comparatively good according to *Lightwood* (9) and mainly depends on the patient developing nephrocalcinosis, in which case the prognosis is bad.

Summary

A case of renal hyperchloremic acidosis (Lightwood) is reported. The patient, a girl 2 years old has suffered from vomiting, loss of weight and constipation for 1½ years. Marked hypersodiemia, hyperchloremia, azotemia and acidosis of the blood, but alkaline urine were found together with signs of renal insufficiency but no nephrocalcinosis. By charging the patient with ammonium chloride by mouth, the pH of the urine did not change. Therapy with sodium citrate was unsuccessful.

A brief discussion of the pathogenesis of the syndrome is followed by the conclusion that the basic changes probably are a primary defect in hydrogen-ion bicarbonate-ion exchange in the renal tubules, together with a primary lesion of the glomerulus.

Acidose rénale hyperchlorémique.

Description d'un cas d'acidose rénale hyperchlorémique (Lightwood). La patiente, une petite fille de 2 ans, avait souffert de vomissements, d'amaigrissement et de constipation durant un an et demi. Elle présentait une augmentation marquée des taux du sodium, du chlore et de l'azote dans le sang ainsi que de l'acidose sanguine, mais les urines étaient alcalines et l'on notait la présence de signes d'insuffisance rénale, mais sans néphrocalcinose. L'administration perorale de chlorure d'ammonium en quantités abondantes n'amena aucune modification du pH des urines. Un traitement par le citrate de soude n'amena aucun résultat. Après une brève discussion de la pathogénèse de ce syndrome, les auteurs concluent que l'origine doit probablement en être attribuée à une perturbation primitive des échanges des ions hydrogène et bicarbonate dans les tubes urinaires en même temps qu'à une altération primitive des glomérules.

Renale hyperchlorämische Azidose.

Ein Fall von renaler hyperchlorämischer Azidose (Lightwood) wird beschrieben. Die Kranke, ein zweijähriges Mädchen, hatte durch 1½ Jahre an Erbrechen, Gewichtsverlust und Verstopfung gelitten. Eine deutliche Vergrösserung des Natrium-, Chlor- und Stickstoffgehalts, Azidose im Blut, aber alkalischer Harn wurden zusammen mit Anzeichen von renaler Insuffizienz ohne Nephrocalcinose gefunden. Perorale Verabreichung von Ammoniumchlorid führte zu keiner Änderung des pH im Harn. Behandlung mit zitronensaurem Natrium blieb erfolglos. Eine kurze Erörterung der Pathogenese des Syndroms führt zur Schlussfolgerung, dass die zugrundeliegenden Veränderungen wahrscheinlich auf einen fehlerhaften Austausch zwischen Wasserstoff und Bikarbonat-Ionen in den Nierentubulis zusammen mit einer primären Läsion der glomeruli zurückzuführen sind.

Acidosis hiperclorémica renal.

Un caso de acidosis hiperclorémica renal (Lightwood). Enferma de 2 años de edad, sufriendo vómitos, pérdida de peso y estreñimiento durante año y medio; marcada hipersodemia, hipercloremia, azoemia y acidosis en la sangre, pero orina alcalótica, junto con señales de insuficiencia renal, sin nefrocalcinosis. La administración de cloruro de amonio por vía oral no modifica el pH de la orina. Terapéutica con citrato de sodio inefectiva. Breve discusión de la patogénesis del síndrome, seguida de la conclusión de que los cambios básicos radican probablemente en un defecto primario en el intercambio de los iones de hidrógeno y de los iones de bicarbonato en los túbulos renales, junto con una lesión primaria del glomérulo.

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PROGRESS IN PEDIATRICS

The Hyaline Membrane Disease

A Review of Earlier Clinical and Experimental Findings and Some Studies on the Pathogenesis of Hyaline Membranes in O_2-intoxicated Rabbits

by R. BERFENSTAM, T. EDLUND and L. ZETTERGREN

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I. Review of Earlier Clinical and Experimental Findings

Hyaline membranes in the lungs of adults have been observed i.a. in viral pneumonia (Ash & Spitz 1945), in pulmonary tuberculosis, rheumatic pneumonia, uremia, after intoxications with carbonyl chloride and nitrous gases (cf. Naish 1928, Tragerman 1936, Epstein & Greenspan 1941, Olesen 1950, Roubier & Plauchy 1934, Doniach 1947, Bass *et al.* 1952, Zettergren 1955). Such membranes have also been found in lung-lesions induced by X-rays (Warren & Gates 1940).

Hyaline membranes in the lungs of infants, sometimes called vernix or asphyxial membranes, have been extensively studied by pathologists, pediatricians and obstetricians.

Hyaline Membranes in the Newborn

Hyaline membranes are said to be absent in the stillborn (Miller & Hamilton 1949, Miller & Jennison 1950, Blystad *et al.* 1951). Among the living newborns the premature infants are most affected. In mature infants membranes are found, especially after asphyxia during labour or after delivery through caesarean section. Other predisposing factors are diabetes in the mother and placenta praevia.

Potter (1953) stated that hyaline membranes are often the only pathological finding at the post mortem examination of newborn infants, who have showed signs of asphyxia.

Blystad *et al.* (1951), and Potter (1953) observed hyaline membrane in 15–25 per cent of mature infants dying within 5 days after birth. In premature infants they found membranes in 50 per cent of the infants, a re-

quency also reported by Harnæs & Torp (1954). Blystad *et al.* (1951) emphasize "that hyaline membranes represent one of the most serious problems of prematurity and that this is probably one of the main factors, which keep the mortality rate of newborn infants at a high level".

Symptomatology

The syndrome associated with hyaline membranes is respiratory distress which may be of an extreme degree. It has been claimed that these infants are apparently healthy at birth and that the respiratory distress develops after a "quiet period" (Johnson & Meyer 1925, Potter 1952, 1953, Gruenwald 1953, Craig 1954, Harnæs & Torp 1954). The length of the quiet period is said to be 1–2 hours (Potter 1953). Gellis (1953), however, maintains that most infants with hyaline membranes never have a normal respiratory function but that they may appear healthy until some hours after birth if they are not observed continuously.

Concomitant with the respiratory distress there is usually a pronounced discrepancy between the forced respiratory efforts of the infants and the auscultatory findings in chest examinations, i.e. progressively weaker breath sounds.

Potter (1953) stated that infants not showing respiratory distress within 12 hours after delivery are beyond the dangerous period. Deaths caused by "the hyaline membrane disease", occur mostly during the first day of life, but can be observed up to 48–72 hours after birth (see for example Blystad *et al.* 1951, Potter 1953).

In "later deaths" the infants often suffer from other debilitating conditions such as malformations, intracranial hemorrhage or erythroblastosis (Harnæs & Torp 1954).

Pathology

Lungs with hyaline membranes are dark red, larger than normal collapsed lungs and have a liver-like consistency. They contain very little air and sink when placed in water (for references cf. Potter 1953). Since the membranes in the newborn are often accompanied by massive atelectasis, Potter (1952) suggested that the condition should be called "resorption atelectasis with hyaline membranes". She based this terminology upon the fact that breath sounds can be heard for a short time after birth, and upon the microscopical picture of the alveoli which does not exhibit the typical intrauterine pattern. Craig (1954), however, from studies of the alveolar epithelium emphazised that its appearance does not permit the conclusion as to whether the atelectasis is primary or secondary since the epithelial appearance can also be correlated with the degree of maturity of the infant.

Ranström (1953) reported that in lungs with hyaline membranes both forms of atelectasis are often found simultaneously and that in the individual case one of the types usually dominates the picture.

Etiology and Pathogenesis

On the genesis of the membranes in the newborn there are the following theories.

1. *The aspiration theory*

The proponents of this theory suggest that aspiration of amniotic fluid before or during labour is a requisite for the formation of hyaline membranes.

Potter (1953) and Snyder (1953) among others report that the foetus may exert respiratory movements in utero. It may be that these respiratory movements can be exaggerated by intrauterine asphyxia leading to gross aspiration of amniotic fluid and cellular debris to the sites where the membranes are formed.

Some authors claim that the membranes are formed from the vernix caseosa (Johnson & Meyer 1925, Farber & Sweet 1931, Farber & Wilson 1932, Ahlström 1942, Claireaux 1953). Other investigators suggested that the membranes are derived from the proteins in the amniotic fluid (Blystad *et al.* 1951, Landing 1953). Wagner (1954) considered that they are formed from mucoproteins in the amniotic fluid which in turn are derived from the upper respiratory tract of the foetus.

Ahvenainen (1953) stated that an admixture of the aspirated amniotic fluid with acid contents from the stomach is necessary for the formation of the membranes.

Some of the authors who claimed that the membranes are formed from the amniotic fluid postulate that this fluid is dehydrated in the lungs and that the dehydrated residue forms the membranes. During membrane formation the cells of the vernix caseosa are supposed to become optically homogenous which should explain why cellular debris is not generally observed in the membranes.

2. *The theory of increased capillary permeability in the lungs*

Benitez (1952), Arey (1953), Gruenwald (1953) state that an increased permeability of the capillaries is caused by anoxia. Gitlin & Craig (1956) concluded that the hyaline membranes found in the newborn infants studied by them consist mainly of fibrin. The above-quoted authors thought that plasma leakage into the structures involved in the membrane formation furnished the building material for the membranes.

3. *The theory of Miller et al.*

Miller & Hamilton (1949) and Miller & Jennison (1950) considered that the hyaline-like material in the lungs is the result of an injury caused by an unknown agent that also causes the premature birth of the infants.

4. *The heart failure theory*

Lendrum (1955) interpreted the clinical and pathological findings in premature newborn infants suffering from "hyaline membrane disease" as manifestation of "left-heart failure" resulting in an over-loading of the thoracic veins and pulmonary

circulation. This overload was considered to be the result of the fact that the cardiovascular system in the premature infants could not be adapted to extrauterine life.

Summarizing it may be said that the etiology and pathogenesis of *hyaline membranes in the newborn* is far from established. Personally we are of the opinion that until more complete studies of the respiratory and circulatory functions and their regulation in these infants have been carried out, speculations concerning the relationship between the formation of hyaline membranes, atelectasis and pneumonia are futile (cf. Johnson 1923; Johnson & Meyer 1925; Hook & Katz 1928; Helwig 1933 for data on "pneumonia in the newborn" together with hyaline membranes). Hyaline membranes as the only finding at the post mortem examination do not prove more than that several pathological processes giving the same histological picture may be the cause of death.

If the hyaline structures are membranes in the physical sense they must interfere with the gaseous exchange in the lungs (Miller 1954, Craig 1954). This may be stated in spite of the opinions of Gruenwald (1953) and Ranström (1953). The latter author regards atelectasis as the main villain in the disturbed gaseous exchange.

Therapy

From the above it follows that the treatment of children suffering from respiratory distress associated with the formation of hyaline membranes must be purely empirical as long as the etiology and pathogenesis is unknown. The common therapeutic methods are reviewed by Gordon (1954) and consist in protecting the foetus and the newborn from supposed precipitating factors and aim to provide an adequate oxygen supply when respiratory distress has developed. Fifty per cent oxygen, preferably saturated with water vapour, is recommended. Emptying of the stomach immediately after birth is also advocated by some authors.

Experimental Production of Hyaline Membranes

Elystad *et al.* (1951) repeatedly injected amniotic fluid into the excised respiratory tract of the guinea pigs. The lungs were alternately expanded and compressed. By this procedure they succeeded in obtaining membranes which were in some respects similar to those observed in infants. Johnson & Meyer (1925) injected amniotic fluid intratracheally in living animals but did not find any membrane formation. In one rabbit, however, they obtained membranes when ovalbumin was injected intratracheally.

Barber (1937), Miller *et al.* (1951), De & Anderson (1954) showed that

cutting of the vagi resulted in pulmonary oedema and the appearance of hyaline membranes in the majority of their rabbits.

For a long time it has been known that oxygen poisoning can cause pulmonary damage (Smith 1899, Schmiedehausen 1909, David 1912, Karsner 1916, reviews by Bean 1945, Ohlsson 1947, Aschan 1948, Pichotka 1950).

Pichotka (1941) and Liebegott (1941) observed structures in the lungs of oxygen-poisoned animals which resembled what now is called hyaline membranes. In a later paper Kühn & Pichotka (1948) were of the opinion that, in oxygen-poisoned animals, membranes were composed of thrombi in the capillaries and necrotic alveolar epithelial cells.

Berfenstam *et al.* (1954) pointed out that the localization and tinctorial properties of hyaline membranes were the same in oxygen-poisoned rabbits as in newborn infants and that in oxygen poisoning the membranes were only one sign of oxygen toxicity. Similar conclusions were made by Bruns & Shields (1951) who suggested that oxygen is a local irritant to the pulmonary epithelium and causes capillary damage. They quoted Chapin & Hohl (unpublished) who reported that unilateral breathing of pure oxygen caused changes in this lung, the controlateral lung which received ordinary air showed no changes.

De & Anderson (1954) found that adult rats and guinea pigs when exposed to oxygen developed hyaline membranes, newborn animals of these species developed membranes and atelectasis.

II. Own Investigation

That the use of high percentage oxygen gas-mixture in the treatment of newborn infants suffering from respiratory distress should be one of the main factors causing the formation of hyaline membranes seems unlikely. It may be, however, that oxygen therapy with such gas mixtures may exaggerate the degree of membrane formation.[1]

In this investigation we decided to study the pathogenesis of hyaline membranes in oxygen-intoxicated rabbits.

Methods

Animals: 77 adult rabbits of mixed breed and of both sexes were used. They weighed 2.0–3.5 kg with an average weight of 2.5 kg. The animals were given food and water *ad lib.* during the experiments.

[1] For prematures the low O_2 tension in utero is their gaseous environment. It may be that the O_2 content of air can induce a sort of oxygen poisoning since they are not prepared for extrauterine life. Since we have a working hypothesis that 70–80 per cent oxygen may be as toxic for adult rabbits as air for prematures, the experiments were carried out on adult rabbits.

Oxygen treatment: A gas chamber with a volume of 0.3 m³ with a tight glass cover was used. Pure oxygen at atmospheric pressure was supplied from a gas cylinder battery, the oxygen concentration in the chamber was maintained at 70–80 per cent. All experiments were carried out at a chamber temperature of 20–23°C, with a relative chamber humidity of 70–80 per cent. A closed circuit containing a pump, water and CO_2 absorbers were connected to the chamber via separate orifices. The electrical motor of the gas pump did not cause ozone-formation.

Histological methods

Fixation and preparation of the histological material: Formaldehyde solution (4 g/100 ml) containing 1.5 per cent methanol was used as fixative. The organs were fixed for 1–10 days before embedding in paraffin or being sectioned with a freezing microtome.

Staining methods: The following stains were used. (The numbers within brackets refer to the relevant sections in Romeis' manual (1948).) Haematoxylin – v. Gieson stain (708); Heidenhain's azan stain (1489); Weigert's fibrin stain (1424); Scarlet red for lipids (1040); Mucicarmine stain for mucus (2025); Kossa's silver nitrate method for calcium (1637); Tiermann-Schmielzer's method for iron (1204); Glycogen stain according to Best (1103); Periodic acid – Schiff reaction (Hotchkiss 1948); Millons reagent for phenolic compounds (Pearse 1948); Hale's colloidal iron stain for acid polysaccharides (Pearse 1948).

Serum carbohydrates: Blood samples were taken from 14 oxygen-poisoned animals immediately before death and from 5 apparently healthy animals which served as controls. Nine of the oxygen-treated animals had hyaline membranes in the lungs.

Duplicate determinations of hexosamine, hexose (apart from blood glucose) and sialic acid were carried out on each serum.

Hexosamine was determined according to Blix (1948), hexose according to Vasseur (1948) and sialic acid according to Svennerholm.[1]

Blood cell counts: In seven animals the erythrocytes and leucocytes were counted: 1) During a period of 2–3 weeks before oxygen exposure. 2) During the stay in the gas chamber.

Results

Behaviour of the animals

After about 48 hours exposition to the oxygen-air mixture the animals began to refuse food and water. The respiratory movements became slow and deep. The rabbits sat quietly, sometimes with their heads in maximal dorsal flexion. These symptoms became more and more pronounced and death took place after 72–144 hours in the gas chamber.

If the animals having this type of respiratory distress were taken out of the chamber this increased their distress and cyanosis and sometimes motor activity was increased. This change of gaseous-environment can, however, be fatal. Death is sometimes accompanied by an acute pulmonary oedema.

When the animals were replaced in the gas chamber the cyanosis etc. was diminished.

[1] We are indebted to Dr. L. Svennerholm, Inst. of Medical Chemistry, University of Gothenburg, for these determinations.

TABLE 1

Hexoseamine mg/ml	Hexose mg/ml	Sialic acid mg/ml
Oxygen poisoned animals		
0.93	0.92	0.91
0.83	0.88	1.00
0.82	1.13	0.76
0.84	0.80	0.86
0.89	1.13	1.18
0.64	0.64	0.74
0.51	0.80	0.93
0.79	1.00	0.82
0.60	0.91	0.90
0.76	1.03	1.06
0.48	0.55	0.60
0.86	0.98	0.84
0.99	1.38	1.14
1.11	1.65	1.25
0.789	0.986	0.928
Control animals		
0.55	0.60	0.56
0.49	0.57	0.60
0.76	0.86	0.93
0.69	0.86	0.87
0.55	0.55	0.66
0.608	0.688	0.724

Post mortem findings

The autopsies were performed as soon as possible after death of the animals. The pleural surfaces were smooth and glistening in spite of the fact that the pleural cavities in some animals contained small amounts of a colourless exudate. The enlarged lungs had a blue-red colour and a rather firm, liver-like consistency (Fig. 1).

In some of the animals the trachea and bronchi contained relatively large amounts of a foamy colourless fluid. From the cut pulmonary parenchyma clear fluid oozed freely when pressure was applied.

The hearts were usually enlarged and the pericardial sacs contained a clear exsudate in some cases. The livers showed signs of congestion and in a few animals free fluid was found in the abdominal cavity.

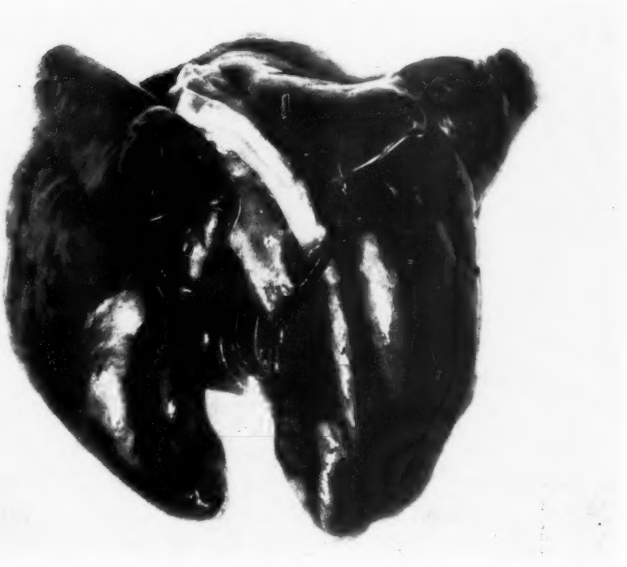

Fig. 1. The lungs of a rabbit which died after five days exposure to oxygen. The lungs are enlarged, dark red, have a liver like consistency. The pleural surfaces are moist and glistening.

Histological findings

In the lungs of oxygen-poisoned animals perivascular oedema, capillary stasis and thrombosis in some capillaries could be seen. Pulmonary oedema was observed as a rule. In the fluid and in the non-oedematus areas some scattered, desquamated swollen epithelial cells as well as a few erythrocytes and leucocytes were found. About 60 per cent of the animals showed atelectasis of varying degree (Figs. 2, 3 and 5).

Eighty per cent of the animals had hyaline membranes, which were most often seen in the respiratory bronchioles, the alveolar ducts and their atria (Figs. 2, 3, 5, 6, 7) and less frequently in the alveoli.

When the membranes were abundant they had a thickness of up to 70 microns and were associated with a more or less pronounced atelectasis. The partially collapsed alveoli usually contained small amounts of a filamentous exsudate, which in some areas had the staining properties of fibrin.

The membranes in the respiratory bronchioles had a continuous tape-like structure. Their luminal borders were usually distinct. The surfaces

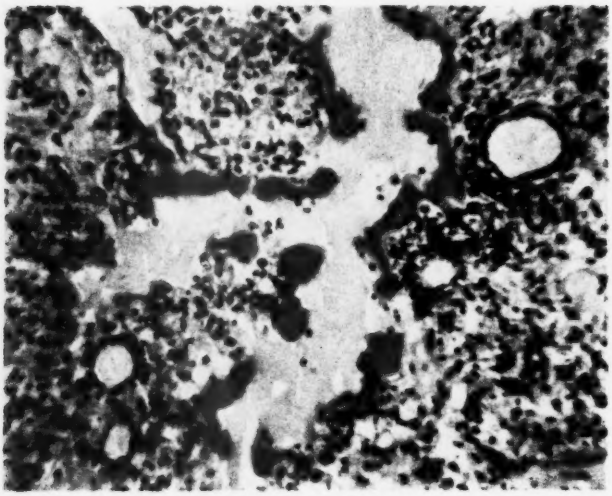

Fig. 2. An alveolar duct with thick hyaline membranes. The parenchyma shows pronounced atelectasis. Periodic acid – Schiff reaction.

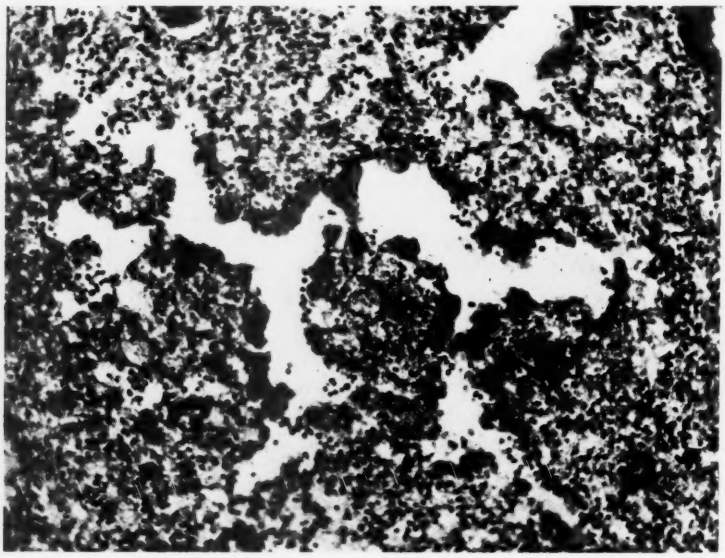

Fig. 3. Alveolar ducts with thick hyaline membranes. In the lumina desquamated epithelial cells and some leucocytes can be seen. Haematoxylin – v. Gieson stain.

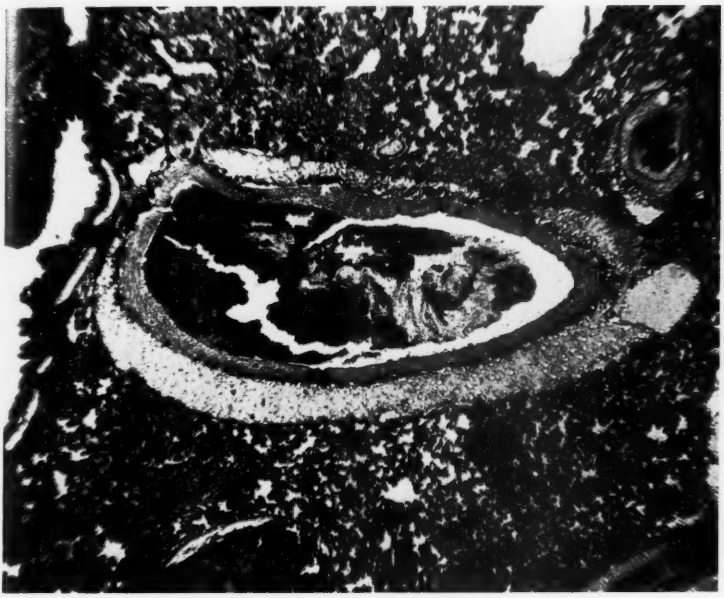

Fig. 4. Pronounced oedema around a pulmonary blood vessel. Haematoxylin – v. Gieson stain.

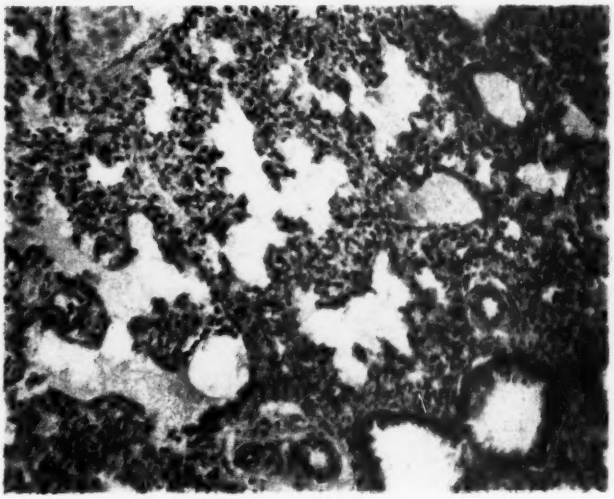

Fig. 5. Alveolar ducts with hyaline membranes. Atelectasis of the parenchyma. Periodic acid – Schiff reaction.

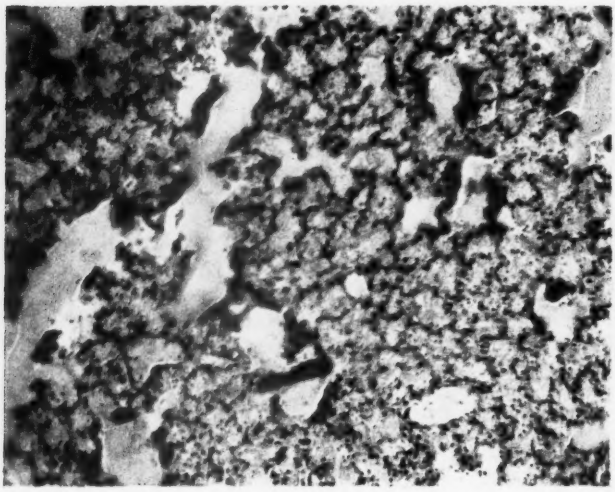

Fig. 6. Hyaline membranes in bronchioli, alveolar ducts and alveoli. The alveoli without membranes contain a thready almost cell-free exudate. No atelectasis is seen. Periodic acid – Schiff reaction.

Fig. 7. Alveolar ducts and alveoli with hyaline membranes. Periodic acid – Schiff reac on.

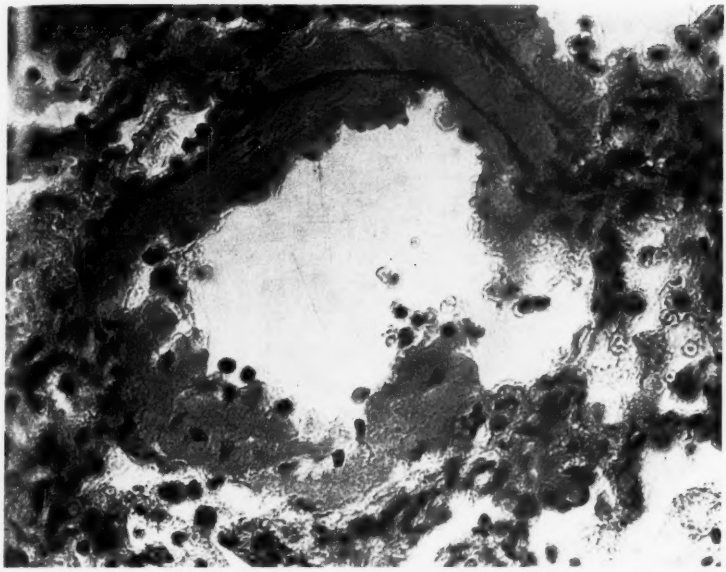

Fig. 8. Hyaline membranes in two alveoli. Scattered epithelial cells and leucocytes in the lumina. The border between these two alveoli consists of a thin, wavy collagenous structure (see top of the figure). Haematoxylin – v. Gieson stain.

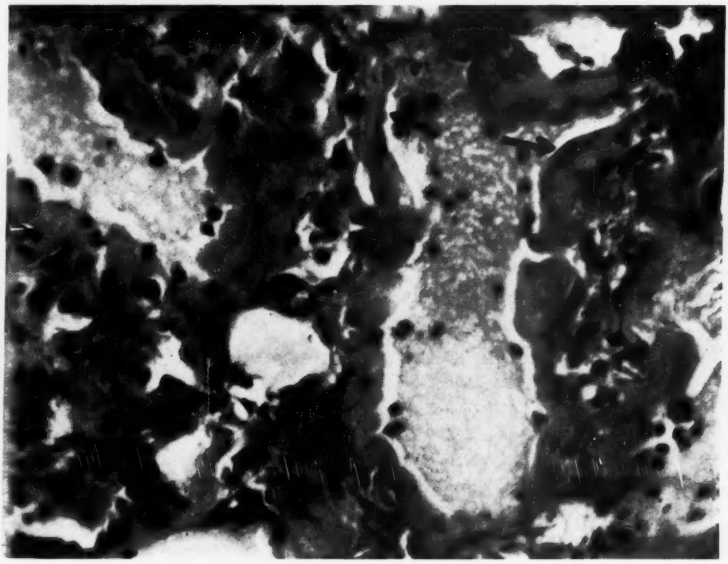

Fig. 9. Alveolar ducts with hyaline membranes. The right arrow shows a membrane covered with swollen alveolar epithelial cell, the left shows a cover of necrotic alveolar epithelium. In the lumen exudate and desquamated epithelial cells can be seen. Haematoxylin – v. Gieson stain.

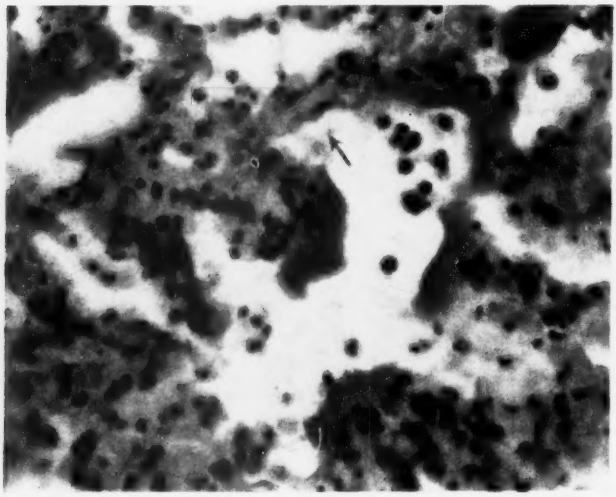

Fig. 10. Alveolus with hyaline membrane. The arrow points to a blood-filled capillary covered by the membrane. Periodic acid – Schiff reaction.

of the membranes were most often smooth but sometimes had a wave-like structure. In the bronchioles the membranes lined the walls, in the alveolar ducts they closely invested the alveolar septa. In some cases we observed that the hyaline membranes were laminated and could be traced to a compact thready exsudate staining like fibrin.

Epithelial cells, erythrocytes and leucocytes were sometimes seen situated close to the surfaces of the membranes or in them (Figs. 3 and 8). In rare cases the membranes were covered with alveolar epithelial cells, which had a swollen to necrotic appearance (Fig. 9). The capillaries were often intact when situated under membranes in an early phase of development (Fig. 10). Sometimes, however, capillary thrombi were seen. Under membranes which were in direct contact with the connective tissue of the bronchial and alveolar walls the capillaries were collapsed and bloodless. In such cases the alveolar septa sometimes showed necrobiotic changes (Fig. 8).

Tinctorial properties of the membranes

The membranes in oxygen-poisoned rabbits are acidophilic and exhibit a yellow to brown-yellow colour with the haematoxylin–v. Gieson stain. The azan stain gives a blue colour. The material forming the membranes does not contain iron, calcium or glycogen in amounts detectable with the stains used by us. The membranes are not stainable with the mucicar-

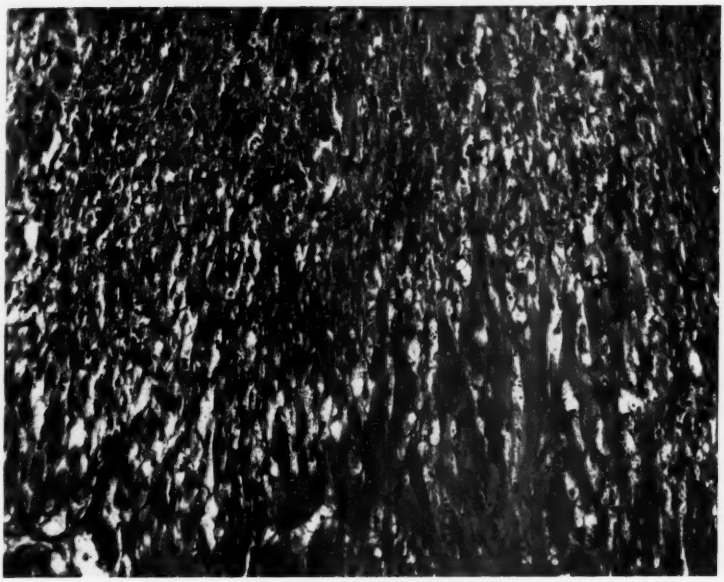

Fig. 11. Myocardium from a rabbit killed with oxygen. Destructed muscular cells and infiltration of lymphocytes and plasma cells. Growth of connective tissue elements. Haematoxylin – v. Gieson stain.

mine stain. Weigert's fibrin stain does not show fibrin in the membranes, but in some cases, thready structures with the staining properties of fibrin are in continuity with the hyaline membranes (cf. Brannan & Goodpasture (1924), Zettergren (1955) for observations where fibrin does not show the typical colour reactions and fibrillar structure). Some membranes show clouds of very small sudanophilic and birefringent droplets.

The hyaline structures show a positive reaction with the periodic acid-Schiff reagent (Figs. 2, 5, 6, 7, 10). Hale's reaction for acid mucopolysaccharides as well as the Millon reaction for phenolic compounds are negative.

Further histological findings

Seven animals had a purulent bronchitis and bronchopneumonia. Fifteen animals had heart lesions consisting of an interstitial, more or less diffuse abacterial myocarditis (Fig. 11).

Serum carbohydrates

The results of the determinations of serum carbohydrates are given in Table 1. Statistical treatment of the data according to common methods for small samples shows that the hexose and sialic acid concentrations probably are higher in the oxygen-treated animals ($P < 0.05$).

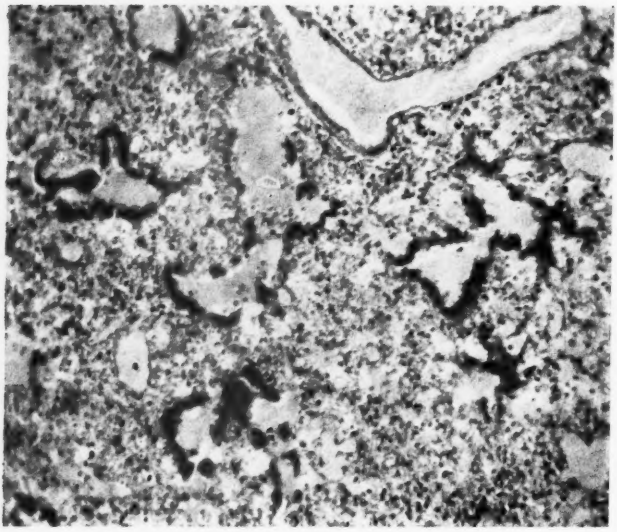

Fig. 12. Lung from a premature infant which died 24 hours after birth. There are some alveoli and alveolar ducts with hyaline membranes. No amniotic debris could be seen in the lungs. Cf. Fig. 5 which shows a similar picture. Periodic acid – Schiff reaction.

Blood cell counts

No differences could be found between the values obtained before and during the oxygen treatment.

Discussion and Conclusions

In this investigation we have studied the development of hyaline membranes in oxygen-poisoned adult rabbits. The localization of the membranes as well as their morphology and staining properties are the same as those found in adult man and newborn infants suffering from the "hyaline membrane disease". The degree of atelectasis is not so pronounced in adult rabbits as in newborn infants. A discussion on the cause of this discrepancy is useless because of the possibilities of variations in the mode of reaction to noxious agents between different animal species, and intra-species variations depending on the age of the individual. Thus no general statement can be made on the temporal and spatial relationship between membrane formation and atelectasis. We think that the earlier literature quoted above, almost certainly excludes the possibility that hyaline membranes in newborn infants are exclusively formed by material derived from

the amniotic fluid. Our findings in rabbits and the results of Gitlin & Craig (1956), who used fluorescin-labelled antibodies as well as conventional histological methods in their study on newborn infants with hyaline membranes seem to indicate that the membranes can be built up by plasma components, including carbohydrates and necrotic alveolar epithelial cells. The pathogenesis might be an increased permeability in the blood capillaries of the lungs leading to an exudation and fibrin-formation in the exudate.[1]

In the oxygen-poisoned rabbits, oxygen-toxicity itself may cause the increased capillary permeability. Another possibility is that CO_2 retention is the cause of the membrane formation, since CO_2 excess can induce hyaline membrane formation in animals (Sehlkopf & von Werz).

Whether the positive carbohydrate reactions in the membranes studied by us are correlated to the probable increase in "stress polysaccharides" (cf. Selye et al. 1953–1955 for references) is impossible to state.

Summary

The earlier literature on the occurrence of hyaline membrane in humans, especially in the newborn is reviewed. The experimental production of hyaline membranes in animals is discussed with regard to the "hyaline membrane disease" in the newborn.

In our own experiments on rabbits the histological and pathological changes induced by lethal oxygen poisoning were studied. It was found that pulmonary hyaline membranes occurred in 80 per cent, atelectasis in 60 per cent and a pronounced abacterial myocarditis in 20 per cent of the animals.

It was shown that the membranes in oxygen-poisoned rabbits had the localization, morphology and the same staining properties as in newborn infants suffering from the "hyaline membrane disease". The microscopical studies revealed that in oxygen-poisoned rabbits the membrane formation was probably preceded by an increased capillary permeability in the lungs and that the material forming the membranes may be classified as plasma components including carbohydrates. Whether the positive carbohydrate reactions in the membranes studied by us are correlated to the probable increase in "stress polysaccharides" is impossible to state. As a conclusion it was suggested that hyaline membranes also in newborn infants may be formed as a sequel to an increased permeability of the blood capillaries in the lungs.

Formation de membranes hyalines dans les alvéoles pulmonaires.

Les altérations histologiques et pathologiques provoquées par une intoxication mortelle par l'oxygène ont été expérimentalement étudiées chez le lapin. La présence de membranes hyalines dans les poumons a été observée dans 80 % des cas, celle d'atélectasies, dans 60 % des cas et celle d'une myocardite abactérienne sévère, dans 20 % des cas. Les membranes hyalines rencontrées chez les lapins intoxiqués par l'oxygène

[1] Gitlin & Craig report that the common histological techniques do not stain fibrin when plasma albumin is not present in a concentration of above 1 per cent. This may explain why hyaline membranes do not become coloured with fibrin stains.

présentaient les mêmes caractéristiques de localisation, de morphologie et de coloration que celles que l'on trouve chez les nouveau-nés atteints de « hyaline membrane disease » (formation de membranes hyalines dans les alvéoles pulmonaires). Les examens microscopiques ont révélé que la formation de ces membranes chez les lapins intoxiqués par l'oxygène était probablement précédée d'une augmentation de la perméabilité des capillaires dans les poumons et que les substances dont ces membranes sont constituées peuvent être considérées comme provenant du plasma et comprennent notamment des hydrates de carbone. Il n'a pas été possible de déterminer si les réactions positives obtenues dans les membranes étudiées en ce qui concerne les hydrocarbures ont un rapport quelconque avec l'augmentation probable du taux des "polysaccharides de stress ». En conclusion l'auteur émet l'hypothèse que la formation de membranes hyalines dans les alvéoles pulmonaires des nouveau-nés pourrait également être la conséquence d'une augmentation de la perméabilité des capillaires dans les poumons.

Die Hyalinmembranenkrankheit.

In Versuchen an Kaninchen wurden die histologischen und pathologischen Veränderungen, die durch lethale Sauerstoffgaben hervorgerufen wurden, studiert. Es ergab sich, dass hyaline Membranen in den Lungen in 80 % der Tiere auftraten, Atelektase in 60 % und eine ausgesprochene abakterielle Myocarditis in 20 %. Es zeigte sich, dass die Membranen bei den sauerstoffvergifteten Kaninchen dieselbe Lokalisation, Morphologie und Farbstoffaffinität aufwiesen, wie bei Neugeborenen mit „Hyalinmembranenkrankheit". Mikroskopische Studien enthüllten, dass bei den sauerstoffvergifteten Kaninchen wahrscheinlich eine vergrösserte kapilläre Durchlässigkeit in den Lungen der Membranbildung vorausgeht und dass das die Membranen bildende Material als Plasmabestandteile mit Einschluss von Kohlehydraten klassifiziert werden kann. Ob die positiven Kohlehydratreaktionen der Membranen, die beobachet wurden, in einer Beziehung zu der wahrscheinlichen Zunahme der „Beanspruchungs-Polysaccharide" stehen, war unmöglich festzustellen. Zum Abschluss wird die Vermutung ausgesprochen, dass auch bei neugeborenen Kindern hyaline Membranen als Folge der gesteigerten kapillären Permeabilität in der Lunge entstanden sein können.

La enfermedad de la membrana hialina.

Estudiáronse, por experimentación en conejos, los cambios histológicos y patológicos inducidos por la intoxicación letal de oxígeno. Hallóse que en un 80 % de los animales, se presentaban membranas pulmonares hialinas, en un 60 % atelectasia y en un 20 % miocarditis abacterial pronunciada. Apareció que las membranas, en los conejos intoxicados con oxígeno, tenían la localización, morfología y mismas propiedades maculosas, que en los niños recién nacidos afectos de « enfermedad de la membrana hialina ». Los estudios microscópicos revelaron que en los conejos intoxicados con oxígeno, la formación della membrana estuvo probablemente precedida por una permeabilidad capilar acrecentada en los pulmones y que el material formando las membranas puede clasificarse como componentes plasmáticos incluyendo los hidratos de carbono. Resulta imposible hacer constar si en los estudios de las membranas, llevados a cabo por nosotros, las reacciones positivas de los hidratos de carbono están correlacionadas con el aumento probable del « stress polysaccharides ». Como conclusión, se sugiere que las membranas hialinas también en los niños recién nacidos, pueden estar formadas en secuela de una permeabilidad acrecentada de los capilares sanguíneos en los pulmones.

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Section of Pediatrics and School Hygiene of the Swedish Medical Association

Meeting at Karlstad, Sept. 14, 1957

Fritz Karlström: **Several uncommon cases of liver enlargement in infants.**

An account is given of four cases with congenital heart anomalies which died shortly after birth. The children were born apparently healthy without heart murmurs. Several days post partum an enlarged liver was detected which grew rapidly from day to day and when the patient died it had become excessively enlarged. Autopsy revealed a congenital and life-vitiating heart anomaly and a pronounced liver stasis. One case presented the classical picture of glycogenic enlargement of the liver: i.e., a colossally hypertrophied liver, produced by excessive deposition of glycogen, low blood-sugar threshold, high and prolonged sugar saturation curve, a blood carbohydrate hardly influenced by adrenalin, and acetonuria. A chemical analysis of the glycogen content in various organs disclosed their greatly enhanced glycogen titer. One case presented the so-called liver hamartoma: in a $1\frac{1}{2}$-month-old child a tumor was detected in the liver site. A trial laporatomy disclosed a fist-sized growth which was readily released inasmuch as it was sharply demarcated from surrounding liver tissues. Microscopically the tumor showed the characteristic picture of hamartoma, i.e., a hodge-podge of liver lobules, bile passages and blood vessels. The uncommon hamartomas can hardly be considered neoplastic but rather an abnormal development of liver tissues within a well delimited area. One case was that of an alimentary fatty liver in a 6-month-old child: for several months the child had been reared on a mixture containing 15 % fat. On admission the liver reached down to the umbilical level and a biopsy puncture revealed an excessively severe fatty liver. When the child was placed on a normal diet the liver became reduced in size, was within normal limits after a month and a half and then contained a moderate amount of fat. With the parents' consent the child was now put on the same dietary mixture which it had been reared on at home. The liver increased rapidly in size and the biopsy puncture again showed marked deposition of fat in the parenchyma. The patient was returned to normal diet and one month later the liver was normal in size as well as in fat content. This case demonstrates how easily and within a relatively short time large amounts of fat may be deposited in the liver and how readily it can be made to disappear only by changing the diet.

Discussion:—*Claes Thorén:* A $2\frac{1}{2}$-year-old boy was admitted to Kronprinsessan Lovisa's Barnsjukhus. At 9 months of age he was hospitalized for the first time with a pronounced liver enlargement. Biopsy puncture from the liver revealed an excessive fattening of the liver without inflammatory involvement. He had not been reared on an especially fatty diet and neither had any regression been noted on a fat-scanty

diet. The liver has shown further increment. The patient's general condition has been relatively good and symptoms of systemic disease are lacking. Fatty stools remain unchanged. The cholesterol level is 270 mg % and total lipids show suggestive high levels. Pancreozymin has been demonstrated in the duodenum. Apparently we are dealing with a metabolic disturbance affecting cellular lipid conversion.—*Jelke* has observed 3 cases of myocarditis isolata (Fiedler) with pronounced liver enlargement. In 3 cases of paroxysmal tachycardia in half, one and a half and 4 months old infants an excessive enlargement of the liver was present in 2 of the cases, 5 and 7 cm respectively below the costal region. In a boy who was 5 years old when first examined, a large abdomen had been present since birth due to an extreme liver enlargement. Biopsy revealed liver cells saturated with glycogen. At 8 years of age the liver had become considerably reduced in size.

T. Thysell: **The forster-child's adaptation difficulties in his new home.**

In the Psychiatric Clinic for Children in Karlstad we have reviewed records of foster-children who have been subjected to examinations during the period Jan. 1, 1956, to Aug. 31, 1957, with a view to ascertaining foster-children's adaptation difficulties. We have besides paid special attention to 12 foster-children, who during the past years have frequented the clinic and been seriously mentally disturbed. We have also compared information concerning foster-children, which will become a part of a separate socio-medical investigation on foster-children which as yet is not concluded. A total of 86 foster-children comprises this study. On the basis of the observations made we may draw the following conclusions: (1) Mentally disturbed, injured and neurotic children and adolescents, all with dissimilar types of foster problems, have in certain cases been placed in foster-homes. Several cases have been mentally improved in these homes and in some cases apparently have become mentally healthy. Younger teenagers with decidedly grave associability have in certain instances been placed in foster-homes where they have gradually acquired an acceptable social behavior. (2) A great number of foster-children with residual mental disturbances and foster difficulties have been able to remain in foster-homes and there they receive profitable care and education. (3) As long as the child remains a foster-child, it should if possible be placed in one and the same home. Repeated changes of foster-home tend to make it very hard for the child to settle down and to acquire fixed and good habits. Change of foster-home occasionally seriously disturbs the child's mental development and health. (4) When, after a careful investigation, a troublesome, neurotic or mentally disturbed child or a teenager is considered suited for change of home environment, one should first of all make an attempt to place it in a foster-home. (5) Our foster-homes for problem children demand a special understanding, solicitude and interest from the authorities entrusted with children's care and they should even be given articulate tokens of appreciation for their valuable humanitarian services both to the individual and the community. (6) From the point of view of the foster-child and the community it is right and proper that the councils for children's care in general should display more generosity and readiness in allocating reasonable compensations for the care of difficult and mentally disturbed children and adolescents in foster-homes. Economic stinginess may, when we are dealing with these children, render it impossible for them to become mentally healthy and socially useful. (7) According to our experience, the placing of foster-children, conducted with caution and sound knowledge, stands a far better chance of succeeding than failing. (8) Many times it appears in-

possible to change consanguinous parents, so that better ones become foster parents. Children of unsuitable foster parents should therefore, at an earlier stage than is now practised, be considered for placement in other foster-homes. (9) According to our experience some instances of admissions to juvenile corrective schools could have been avoided if the councils for children's care had intervened at an earlier stage and separated the child from the unsuitable foster-home. (10) The observations which we have had opportunities to make on those foster-children who were referred to us because they became a part of a separate socio-medical investigation of foster-children have in certain cases been so alarming, that they have led us to question of the present organization for the superintendence of foster-children is adequate.

DISCUSSION:—*B. Vahlquist:* Have any special measures been taken to procure suitable foster-homes for children with more severe behaviour disturbances?

K. B. Björnesjö and F. Karlström: Prothrombin determination in infants; comparison between Quick-Lehmann's and Owren's methods.

Sundblad's micro-modification of Owren's method has been tried on a material of infants and has been compared with Quick-Lehmann's method. Parallel determinations have been made with both methods on 40 infants partly during the first and partly during the third–fourth day after delivery. The average prothrombin value during the first day was 27 %[1] with Owren's method and 67 %[1] prothrombin index with Quick-Lehmann's method. In other trials the corresponding figures were 35 %[1] and 73 % respectively. The relatively insignificant fall in prothrombin index in relation to prothrombin percent with Owren's method depends on the slight sensitivity of the Quick-Lehmann's method by moderate falls in prothrombin content. The latter method is on this account not useful as a sensitive liver function test to differ from Owren's method.

In micro-prothrombin determinations in children during the newborn period both methods give too low values unless correction is made for the high hematocrit values in these children. The present investigation has shown that a simple, rectilinear connection exists between the prothrombin percentage according to Owren on the one hand and the hematocrit value and the plasma volume respectively in the reaction mixture on the other hand. This makes possible a simple correction to a normal hematocrit value according to the formula $(100 - Hn)/(100 - H)$, where Hn signifies the normal hematocrit value (in our material 42 %) and H the actual test hematocrit value. This formula has been used for correction of the prothrombin values in a material of infants in varying ages. In newborn children (average hematocrit value 70 %) the prothrombin content according to Owren was 33 % before and 65 % after correction. The correction is therefore necessary at this age if one desires an exact prothrombin value. After one month of age the correction proved to be of less significance in a normal material inasmuch as the hematocrit values do not deviate considerably from those in adults. In cases where the hematocrit values diviate significantly as in anemias and polycythemias the correction should be made even in micro-prothrombin determinations in older children.

DISCUSSION—*B. Vahlquist:* It appears to me as if the hematocrit value of 70 % in the newborn infant lies remarkably high. One usually reckons with 55–60 %. —

[1] These values have not been corrected for hematocrit variations.

K. B. Björnesjö: The average value was obtained in 30 children in whom material for hematrocit and prothrombin were removed from the same finger puncture, and this value should therefore be used for correction in our material. The employed technic for hematocrit determination has been to suck op blood in heparin-rinsed capillary tubes which are sealed and centrifuged for 5 minutes in an international hematocrit centrifuge having a speed of 10,000 r.p.m.

K. D. Rabo: **Phenopromin treatment of nocturnal enuresis.**

The author accounts for personal experiences with a phenopromin derivative in the treatment of enuresis in among others 96 ambulant cases on the Children's Psychiatric Clinic in Karlstad during 1953–56, who were given Psykoton R (methylphenopromin). The customary initial dose for children above 6 years of age was 1 tablet at bed-time and half a tablet when awakened at 22–23 o'clock. The evening dose should not be given before the child is in bed, when otherwise one may experience falling-asleep difficulties. Mothers are instructed to note down daily if the bed has been dry, wet or soupy both at awakening and the following morning, and also to note the depth of sleep. The psykoton dosage varied according to the response to treatment, with increased evening dose if the child was aroused with difficulty or was wet already on awakening, and increased night dose if the bed was wet in the morning. Optimal dosage was most often 1 plus 1 tablet, in certain cases 2 plus 2 tablets. The majority of patients were intensive bed-wetters who proved refractory to treatment with other pharmaceutical, regimentary and milieu changes, etc. Only 6 patients proved refractory even against psykoton treatment, while approximately 70 % quickly became completely dry without further treatment or kept themselves practically dry during the treatment period, which in some cases extended to one and a half years. Only 6 patients presented untoward effects with effective dosage: gastric pains, restless sleep; on the other hand there were no abstinence symptoms. The older children especially often displayed a significant improvement in the general psychic condition, which seemed secondary to the discharge of the psychic pressure which the enuresis had produced.

Discussion.—*Erik Rabo* has treated some 70 cases of enuresis with phenopromin in relatively large doses and often over long periods. A number of cases were discussed who during one or more periods had received placebo tablets and in which bed-wetting occurred almost nightly during this procedure. In spite of the fact that these children had lost faith in the therapy during the placebo trials, they became dry again with phenopromin. Thus it is evident that the excellent effect of phenopromin is not of a psychological nature.—*H. O. Mossberg:* In Västervik's Children's Department we have tried Sandoz' preparation Belladenal R (phenemal plus the total alkaloids from Folium belladonnae) with the same results as reported by Rabo with Psykoton R (phenopromin). Enuresis ceased in 64 %, improved in 28 %, and no effect was noted in 8 %. Total number 39 children. Resemblance in therapeutic results with dissimilar preparations suggests that the pharmacological effect of the chemical—if such a significant effect is present—is not the essential factor. It is quite probable that the form of psychotherapy which is employed during the conversation with the mother and the patient is far more important.

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BOOK REVIEWS

Fritz Souchon: **Therapie mit ACTH, Cortison und Cortison-Derivaten bei Kinderkrankheiten.**

109 pages, 20 figs. and 3 tables. Ferdinand Enke Verlag, Stuttgart, 1956. Price, DM 21.

The author presents a review of treatment with ACTH and cortisone partly on the basis of personal experience in the Children's Clinic in Bremen and partly from a study of an extensive literature on the subject. After introductory remarks about the mode of action of various hormones the author proceeds with a specific account of the therapeutic usefulness of ACTH and cortisone respectively and cortisone-derivatives preparations in most diseases within the internal medical and surgical field as well as on the wards of premature and newborn infants. He stresses especially the usefulness of these preparations in severe infections including tuberculosis, peritonitis and burns, naturally in combination with suitable antibiotics or chemotherapeutic agents. He even emphasizes the usefulness of intravenous ACTH treatment in centrally released disturbances affecting temperature, respiration and circulation. The book is factual, easily read and can be recommended as a handbook for all physicians engaged in pediatrics.

Anna-Lena Bergström

Wissenschaftliche Verhandlungsbericht der Kinderärztetagung der Deutschen Demokratischen Republik in Halle.

Verlagsbuchhandlung Georg Thieme, Leipzig, 1957. 240 pages, 114 figures. Price, DM 23.20.

This pediatric meeting, May 31 to June 2, 1956, was headed by Prof. J. Dieckhoff in Halle. It was attended not only by pediatricians from East Germany but also by prominent pediatricians from the universities of West Germany and representatives from Hungary and Czechoslovakia. The transactions contain reports of about 40 papers dealing with various kinds of pediatric problems with summaries of the discussions.

Ronald S. Illingworth: **The Normal Child.**

J. & A. Churchill Ltd., London, 1957. 356 pages, numerous figures. Price, 33/-.

This book is intended to describe the problems which arise in the normal child in his first five years of life. There are biological variations in the normal child which, if improperly managed, may cause a great deal of worry to the parents. It sets out to give the doctor as much guidance as possible in the management of simple behaviour problems, such as any doctor concerned with the care of children ought to be able to deal with himself. A section is devoted to the prevention of infections and so to the preservation of health. Every normal child has behaviour problems and the author feels that a child with no such problems would be highly abnormal. The opinions ex-

pressed are not always in accord with those of the general pediatric world. The book should be most useful for the doctor working in child welfare centers. It deals with all problems, minor and major, that he encounters in his daily work. Apparently the book is much appreciated among the author's countrymen since the first edition printed in 1953 was reprinted one year later and is now followed by a new editon. In this second edition several chapters have been re-written and due consideration has been paid to new knowledge and new experience.

G. Glogowski: **Die heutige Behandlung der Skelett-Tuberkulose des Kindes und des Jugendlichen.**

Georg Thieme Verlag, Stuttgart, Germany, 1957. 61 pages, 54 figures. Price, DM 12.

This book is the report of ten years of experience with antibiotic treatment of bone and joint tuberculosis in the orthopedic clinic at Münich (Prof. M. Lange). The aim of the book is to promote early diagnosis and to improve the efficacy of systematic early treatment of bone and joint tuberculosis in children and adolescents. Tuberculous spine, coxitis and gonitis are dealt with in separate chapters as well as tuberculosis of the ileum, sacro-iliac joint and of the foot and upper extremity. The old conservative methods of treatment are first used together with streptomycin and isoniazid in order to build up a satisfactory bodily resistance. The blood sedimentation rate falls and the gamma-globulin increases. Abscesses are removed. Then more active surgical therapy is introduced. The risk of hematogenous spread by operation is now insignificant. If it is possible to fix an early diagnosis in cases of joint tuberculosis then the object of the treatment should be to restore complete motility of the joint. The book gives due consideration to opinions and experiences of others.

Erratum

In the September number (Vol. 46, No. 5) we regret that Figures 1 and 2 in Paulin & Mannerheimer, "Heart Murmur in Children", were misplaced. These should be interchanged so that the figure-text on page 400 ("Fig. 1. Phonocardiogram, girl, 8 years ...") applies to the figure on p. 441 and vice versa.

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From the Pediatric Clinic, Karolinska Sjukhuset, Stockholm

Impaired Calcium-Phosphate Homeostasis in Newborn Infants of Diabetic Mothers

by R. ZETTERSTRÖM and R. G. ARNHOLD

Infants of diabetic mothers show many features which are usually associated with prematurity. Of course, many such infants are immature if judged by gestational age rather than by birth-weight. However, in some respects, they behave like more immature infants than their gestational age would indicate. They are usually very edematous, their electrolyte balance resembles that of very premature infants (Zetterström & Åberg, Stapleton), there is a high incidence of hyperbilirubinemia (Zetterström, Strindberg & Arnhold), and they often suffer from the hyaline membrane syndrome (Cardell; Winter & Gellis).

The purpose of this report is to demonstrate that newborn infants of diabetic mothers also may exhibit other features which suggest functional immaturity. Studies of the concentrations of calcium and phosphate in the serum during the neonatal period have provided evidence that the regulation of calcium phosphate homeostasis is impaired in the same way as in prematures (cf. Bruck & Weintraub), i.e. there is a marked tendency to the development of hypocalcemia and hyperphosphatemia.

Material and Methods

The calcium and phosphate homeostasis was studied in nineteen newborn infants of diabetic mothers. For technical reasons only the serum calcium level was followed in some of the patients. The serum phosphate levels were therefore analyzed in only 12 infants.

The gestational age of about 50 per cent of the infants studied was 35–36 weeks, the rest was born at a fetal age of 37–40 weeks. Seven of the pregnancies terminated by normal spontaneous delivery, cesarean section was performed in the rest. The birth-weight of all patients exceeded 3000 g. The period of withholding fluid and food after birth varied between 24 and 48 hours depending on the general condition of the infant. Two of the patients expired with symptoms suggestive of kernicterus, the others were discharged in good condition.

Venous blood was drawn from the internal jugular or femoral vein. The blood was

TABLE 1

Serum levels of calcium and phosphate during the neonatal period in infants of diabetic mothers.

	Age				
	1 day	2 days	3 days	4 days	5–6 days
Calcium, mg per 10 ml 19 infants studied					
Average value	8.5	8.5	8.7	8.7	9.5
Range	6.6–10.7	7.5–9.6	7.3–11.0	7.8–9.6	8.9–10.2
No. of determinations . .	13	10	7	5	8
Phosphate, mg per 100 ml 12 infants studied					
Average value	10.9	11.8	11.9		9.5
Range	9.1–14.9	9.0–14.0	8.2–14.9		6.8–11.2
No. of determinations . .	10	6	10		6

allowed to clot before centrifugation and subsequent separtion of serum. Serum calcium was estimated as described by Biering and serum phosphate according to Youngberg & Youngberg.

Results

The serum concentrations of calcium and phosphate during the neonatal period in infants of diabetic mothers are shown in Table I. The average values for the serum calcium levels were rather low during the first four days of life though the range was rather wide. During the fifth day of life there was a tendency to increased concentrations. Hypocalcemia, i.e. a serum calcium level below 8 mg per 100 ml, was observed at least once in 9 out of the 19 infants studied, i.e. in nearly 50 per cent of the material.

There was no significant difference between the infants with a gestational age of 35–36 weeks and those born after more than 36 weeks of intrauterine life. The levels were also rather constant independent of the duration of withholding fluid and water. The material was too small to permit statistical analysis. However, a difference was found when the infants which were born by spontaneous delivery were compared with those delivered by cesarean section. In the first group, hypocalcemia was observed in one patient out of 7, in the second in 9 out of 12. The increased incidence of hypocalcemia in infants delivered by cesarean section coincides with the results obtained by Gittleman, Pincus, Schmerzler & Saito.

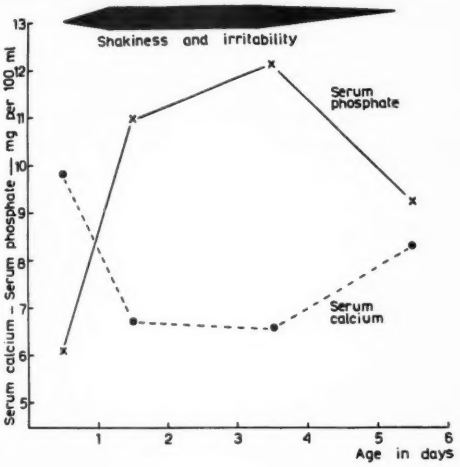

Fig. 1. The concentrations of calcium and phosphate in the first days of life in an infant of a diabetic mother. Delivered at a gestational age of 35 weeks by cesarean section. Birth-weight 3400 g. Fluid and food were withheld for the first 24 hours. On the second day of life the infant was given 50 g of human milk, the amount given was then increased by 50 g per day.

The concentration of phosphate attained rather high values during the first days of life, especially on the second day after birth (Table 1). After the first few days, the levels showed a tendency to fall. It was not possible to correlate the serum phosphate level either with the gestational age or with the mode of delivery. On the other hand, the serum phosphate concentration showed a tendency to rise particularly high in those infants who had starved for more than 24 hours.

The changes in the serum chemistry which are characterized by a high concentration of inorganic phosphate and a low calcium level are consistent with a diagnosis of tetany of the newborn (cf. Bakwin). In fact, several infants showed some symptoms possibly related to tetany, particularly on the third day of life. In one infant convulsions occurred on the third day of life in the presence of a low serum calcium concentration (7.4 mg per 100 ml) and a high serum phosphate level (14.0 mg per 100 ml). The blood sugar was normal. More common signs were twitching of the legs and arms, excessive irritability, and, in a few instances, attacks of cyanosis which could not be explained as the result of respiratory insufficiency, brain lesion, or hypoglycemia. Many infants had tremors and were conspiciously shaky.

Serum concentrations of calcium and phosphate during the neonatal period in one baby born to a diabetic mother are shown in Fig. 1. The infant exhibited mild symptoms suggestive of tetany. It was shaky and highly irritable, and the arms twitched occasionally. The serum calcium concentration attained its lowest level at the same time as the serum phosphate reached its peak.

Comment

At the present time there is no adequate explanation for the poor prognosis in newborn infants of diabetic mothers. Many of the difficulties may be explained in terms of adrenal hyperactivity (Björklund & Jensen; Farquhar) but the whole bizarre complex of varying biochemical and anatomical changes is difficult to interpret solely on this basis. A chemical abnormality such as the retention of fluid and sodium (Zetterström & Åberg) seems to be consistent with this theory; the marked tendency toward acidosis (Lowry, Graham & Tsao) is more difficult to reconcile with this suggestion. The high incidence of hyperbilirubinemia (Zetterström, Strindberg &Arnhold) is more in harmony with the view of functional immaturity or even a hypothyroid state (cf. Åkerrén). In this connection Silver's recent observations of low butanolextractable iodine levels in these infants are of great interest. The marked and rapid drop of the blood sugar level within the first two hours after birth (Farquhar) points to insular hyperactivity.

The pathogenesis of hypocalcemia in association with hyperphosphatemia is even more difficult to explain. Various etiologic factors have been proposed for hypocalcemia of the newborn, such as large dietary intake of phosphate (Gardner, MacLachlan, Pick, Terry & Butler), parathyroid hypofunction (Gardner) and prematurity (Bruck & Weintraub). Since hypocalcemia occurred in our patients despite complete starvation, phosphate intake as a factor can be ruled out. This conclusion is in agreement with the findings of Dodd & Rapaport. Bruck & Weintraub found that the serum calcium level was very labile and frequently low in prematures but remarkably stable in healthy full term infants. Two of their patients with hypocalcemia were infants of diabetic mothers. Elevation of serum phosphate might be responsible for the development of some degree of hypocalcemia but this mechanism is unlikely to be the only cause. On the basis of the finding of a high incidence of hypocalcemia in infants subjected to stress before and during delivery, Gittleman *et al.* advanced the hypothesis that the decrease of the serum calcium level might be accounted for by adrenocortical hyperfunction. The higher frequency of hypocalcemia in prematures was interpreted as a consequence of the fact that the concentration of adrenocortical steroids attains its peak in maternal plasma at the time of premature birth. Hyperphosphatemia might be an additional cause. It may be significant that the symptoms suggestive of tetany which were seen in some of the babies were most pronounced in those infants who were starved for two days. From the finding that the serum urea concentration was particularly high in infants subjected to stress from prolonged labor or from other factors, McCance & Widdowson suggested that such situations give rise to tissue destruction.

This process would also cause the release of phosphate into the plasma. It seems logical that starvation, acting through this mechanism, could thus give rise to hyperphosphatemia.

The findings reported may have some clinical implications. Attacks of cyanosis or convulsions occurring during the neonatal period in babies born to diabetic mothers may be attributed to tetany of the newborn. The fact that zonular cataract has been observed in children born to diabetic women (Granström) also points to a disturbance in calcium metabolism. Since tremor, marked irritability, and twitchings seem to be more frequent when the period of starvation is longer than one day, probably due to an increase of the serum phosphate level, food should not be withheld longer than necessary.

Since many of the features which may be found in newborn babies of diabetic mothers, such as hypocalcemia, hyperbilirubinemia, retention of fluid and sodium, and the occurrence of hyaline membranes, may be related to functional immaturity, these facts should be considered when interruption of the pregnancy is suggested for other reasons. The fact that hypocalcemia is prone to occur in instances of complicated delivery is another point to be considered in the obstetrical management of diabetic women.

Summary

Hypocalcemia together with hyperhosphatemia occur commonly in newborn infants of diabetic mothers.

It is suggested that these features are expressions of functional immaturity of the organism.

The clinical implications of these findings have been discussed. The high incidence of tremor, hyperirritability and twitching in newborn infants of diabetic mothers may be related to hypocalcemia associated with hyperphosphatemia.

Altération de l'homoeostasie du phosphate de calcium chez les nourrissons nouveaux-nés de mères diabétiques.

Une hypocalcémie, ensemble avec une hyperphospatémie, surviennent couramment chez les nourrissons nouveaux-nés de mères diabétiques. Il a été suggéré que ces caractéristiques sont des expressions d'une immaturité de l'organisme. Les implications de ces recherches ont été discutées. L'indice élevé de tremblements, d'hyperirritabilité et de clonisme chez les nourrissons nouveaux-nés de mères diabétiques peut être apparenté à une hypocalcémie, associée à une hyperphosphatémie.

Beeinträchtigte Kalzium- und Phosphathomöostasis bei Neugeborenen zuckerkranker Mütter.

Herabsetzung des Kalzium mit Erhöhung des Phosphatgehalts im Blut kommt gewöhnlich bei neugeboren Kindern diabetischer Mütter vor. Die Vermutung wird ausgesprochen, dass diese Symptome der Ausdruck einer funktionellen Unreife des Organismus seien. Die aus diesen Befunden sich ergebenden Folgerungen werden

erörtert. Die Häufigkeit von Tremor, Überreizbarkeit und Zuckungen bei neugeborenen Kindern von zuckerkranken Müttern mag möglicherweise mit der Hypokalzämie und Hyperphosphatämie verbunden sein.

Homoestasis defectuosa del calcio-fosforo en el neonato de madre diabética.

Los recién nacidos, hijos de madres diabéticas, presentan generalmente hipocalcemia acompañada con hiperfosfatemia. Se sugiere que estas dos características corresponden a una manifestación de inmadurez funcional orgánica. Discusión de las inferencias deducidas de estos hallazgos. La alta incidencia del temblor, hiperirritabilidad y crispaturas en los recién nacidos de madres diabéticas, pueden estar en relación con hipocalcemia asociada con hiperfosfatemia.

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Hemolytic Episodes as the Cause of Jaundice in Children with Allergic Disease.—"Allergic Jaundice"

by M. BARR, S. KRAEPELIEN and R. ZETTERSTRÖM

Acute attacks of jaundice during the course of more or less severe allergic reactions have repeatedly been described (Alvarez; Ferrabouc & Jude; Flandin & Vallery-Radot; Schmengler). For instance, Ferrabouc *et al.* have reported a case with fish allergy, the ingestion of such food causing urticaria, angioneurotic edema, arthralgia and icterus. The concomitant occurrence of jaundice in association with other, more frequent allergic reactions, have been considered caused by liver cell injury (Schmengler) or by allergic spasms within the biliary tract (Alvarez).

This paper presents the clinical features of two children with allergic disease (asthma, allergic rhinitis and eczema) associated with acute attacks of jaundice following exposure to certain antigenic substances. It will be concluded from these cases that the cause of the icterus was acute hemolytic episodes.

Case Reports

Case 1.—B. T., a 13-year-old boy admitted for "allergic work up". Among both paternal and maternal relatives history of asthma and allergic rhinitis. Past history non-contributory except for his allergic symptoms. The present illness started at two months of age with allergic eczema when given juices. Asthma started when he was 3 years old and since that age he has had asthmatic attacks every year, especially in the spring, when he often also had allergic rhinitis. He has turned icteric on several occasions after eating carrots. The parents do not know when this reaction first occurred.

Physical examination on admission did not reveal any remarkable findings. The results of some of the laboratory investigations are included in Table 1.

Intracutaneous testings were positive for house dust and pollen of the kind most common in Sweden during spring and summer.

Following the exposure to pollen of moon-daisy (*Chrysanthemum leucanthemum*) he suddenly got fever, nausea, vomiting and diarrhoea. One day later he felt completely well but the serum bilirubin concentration was found to be 1.3 mg per 100 ml, the bilirubin almost quantitatively being of the indirect type. The jaundice disappeared

TABLE 1

Principal hemotologic data on admission of the patients studied

	Case 1	Case 2
Hemoglobin, g per 100 ml	14.4	10.1
Red blood cells, m. per cmm		3.7
White blood cells, per cmm	5,400	5,900
Eosinophils, per cent of WBC	10	12
Reticulocytes, per cent	0.6	4.0–6.0
Mean erythrocyte diameter, microns	6.9	6.0
Osmotic fragility without previous incubation:		
Hemolysis starting	0.46	0.80
Hemolysis complete (per cent saline)	0.32	0.30
Serum-iron, microgram per 100 ml		113
Life span of the patients' red cells according to the labelled chromium method, days (cf. Fig. 3)		40–50
Serum-bilirubin, mg per 100 ml		2.4
Electrophoresis of the hemoglobin		Motility as normal adult hemoglobin
Antiglobulin test of Coombs:		
direct	neg.	neg.
indirect	neg.	neg.
Thymol turbidity test, units	0.8	2.0
Paper electrophoretic analysis of the serum proteins	normal pattern	normal pattern

shortly and the reticulocyte level, which had been up to 1.3 per cent decreased to 0.6 per cent. A new attack of exactly the same type was produced by the inhalatory provocation test for tree pollen. Following the scratch test for carrots the allergic reaction associated with jaundice recurred, at which time the total serum bilirubin level increased from 0.8 to 2.5 mg per 100 ml (the indirect reacting fraction rising from 0.7 to 2.2 mg per 100 ml). At the same time the hemoglobin level fell from 11.6 to 9.8 g per 100 ml and the relative number of reticulocytes increased from 0.6 to 3.3 per cent (cf. Fig. 1).

Case 2.—A.-M. S., a seven-year-old girl admitted because of asthma, eczema and attacks of jaundice after eating cucumber.

One aunt has attacks of urticaria, one sister gets eczema from cod liver oil. Otherwise the family history was unessential and no hemolytic disease was known for at least three generations past among paternal and maternal relatives. Both the parents and the single sibling have normal hemoglobin levels, the red blood cell diameter and the resistance of the red cells to hypotonic saline also being normal.

The patient had been given cod liver oil during her second and third month without any reaction. At the age of 6 months she had turned icteric after exposure to the smell of fried fish. When starting on formula at 9 months of age she got another attack of

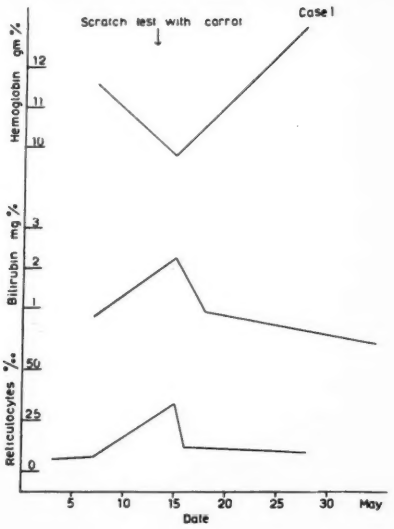

Fig. 1. Case 1. Shows the concentration of bilirubin in the serum (almost quantitatively of the indirect reacting type), the hemoglobin level, and the relative number of reticulocytes after scratch test for carrot.

jaundice, the serum bilirubin level being 3.0 mg per 100 ml. On that occasion the mean red blood cell diameter was 6.1 microns. When the red cells were subjected to hypotonic saline, hemolysis started at 0.48 and was complete at 0.26 per cent sodium chloride. During subsequent years she has had minor attacks of jaundice. However, at the age of 4 years she had a severe attack following ingestion of cucumber. During the first 4 hours she was free from symptoms but then she had fever, nausea, vomited and was agitated. This state lasted for about 18 hours when she felt completely well. Twenty-four hours after the ingestion of cucumber she passed dark urine for one day. At the same time she turned icteric. During the subsequent 12–24 hours the jaundice increased, after that it gradually disappeared within a fortnight. The same type of reaction has also been observed following the ingestions of a special kind of candy, mushroom cooked with cream, and fish. Besides this allergic reaction, she has a history of asthma, allergic rhinitis and eczema following the exposure to egg, tree pollen, feather, dog or cat. Even after a severe reaction following exposure to these last-mentioned allergens she does not develop jaundice. Nor does she get any asthma or allergic rhinitis after eating cucumber or mushroom. Several days before entering the hospital she had a minor attack of jaundice.

Physical examination on admission revealed a normally developed girl with slight symptoms of pulmonary emphysema. The skin was dry, with chronic eczematous changes over the knee joints and the elbows. The sclerae were slightly icteric. There was no hepato-splenomegaly. For laboratory investigations, see Table 1.

Two months after admission when given a small piece of cucumber she got a rather slight reaction. Thrombocytopenic and leucopenic indices did not show any significant changes. However, the hemoglobin level decreased from 10.6 to 8.9 g per 100 ml, and the concentration of bilirubin in the serum increased from 2.3 to 3.6 mg per 100 ml, only minute amounts were of the direct reacting type. The relative number of reticulocytes increased from 5.6 to 13.2 per cent (see Fig. 2). No oxyhemoglobin was found in

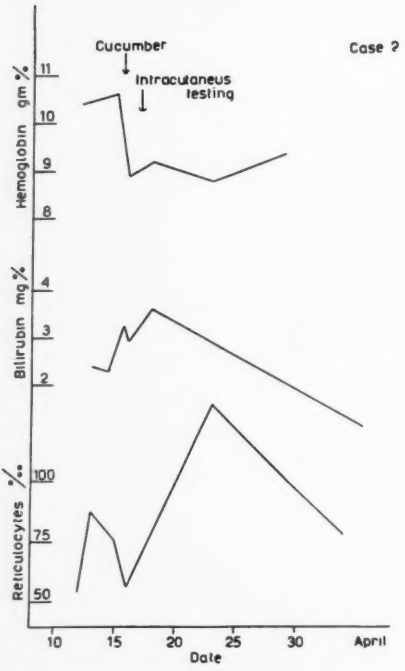

Fig. 2. Case 2. Shows the concentration of bilirubin in the serum (almost quantitatively of the indirect reacting type), the hemoglobin level, and the relative number of reticulocytes after ingestion of cucumber, and after intracutaneous testing.

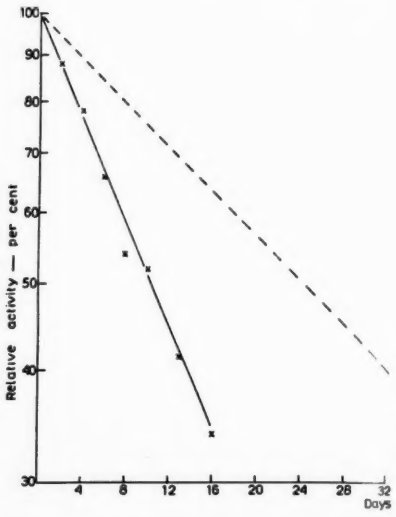

Fig. 3. Case 2. Life-span of the patient's own red cells as studied with the aid of the labelled chromium method. As is evident from the figure, there was a marked shortening of the survival time. The red cells were labelled *in vitro* and afterwards reinjected. ————, for normal cases (Gray and Sterling); × —— ×, patient (Case 2).

the serum by spectrophotometric examination. In order to get information about the hemolytic rate, the endogenous carbon monoxide production was estimated according to Sjöstrand. This investigation revealed a slight but not diagnostic increase during the "cucumber test". Coombs' test, both direct and indirect, was negative both before, during, and after the "cucumber test".

Estimation of the survival time of the patient's own red cells according to the labelled chromium method of Gray & Sterling showed a shortening of the life-span, even when there was no known exposure to allergens (see Fig. 3). This finding indicates the presence of a slight chronic hemolytic disease, which, however, exacerbates during the course of exposure to cucumber as revealed by the development of jaundice and drop of the hemoglobin level.

Comments

Both cases reported present a history of allergic disease and attacks of jaundice after the ingestion or inhalation of small amounts of special foods or pollens. The investigation of the patients revealed that the attacks of jaundice in both cases are due to hemolytic episodes, i.e. there is a drop of the hemoglobin level, raising serum concentration of indirect reacting bilirubin, and subsequent reticulocytosis. The laboratory investigations of our patients did not reveal any evidence of liver cell damage as the causative mechanism of the development of jaundice.

In Case 1, the hemolytic episodes seem to be due to some type of allergic reaction, since it may be provoked by minute amounts af allergens. In Case 2, the situation is more complicated. The patient has had symptoms of intermittent hemolytic disease since the age of 6 months. Estimation of the life-span of the patients own red cells gives evidence of a constantly increased hemolytic rate. The resistance of the red cells to hypotonic saline was found to be decreased as in spherocytosis. Probably, repeated exposure to small amounts of antigens causing hemolysis may have been responsible for the development of a mild chronic aquired hemolytic anemia (cf. Dameshek & Schwartz) which exacerbates following massive exposure to antigenic substances. However, since, in this patient, exposure to pollen which causes a rather severe asthma or allergic rhinitis does not give rise to an acute hemolytic episode, different allergens may be responsible for varying types of reactions.

The symptomatology in the two cases reported resembles that found in favism (for relevant references see Luisada and Marcolongo), but usually the hemolytic reaction is more pronounced in favism than in our patients. In favism, the hemolytic process is induced by the ingestion of fava beans (*Vicia fava*) or by the inhalation of pollen from the blossom of the fava plant. This disease, which was formerly widely distributed in the Mediterranean basin, has also occasionally been observed in the United Kingdom and in the United States among ancestors from the Mediterranean area. Some few cases have been reported among individuals of other extraction (for instance, in China (Du, 1952)). Murana has pointed out the high frequency of other allergic manifestations in families with cases of favism. Furthermore, in favism the sensitivity may not be absolutely specific for the fava bean. Surinyach has found that prickly pears, and Marcolongo that peas, pomegranade and vetch may cause the same type of hemolytic disease as in favism among relatives of some patients known to be sensitive to fava beans.

The resemblance between our cases and the findings in favism supports

the conclusion that the hemolytic episodes causing acute jaundice are due to allergic reactions. However, the mechanism of this reaction still remains obscure. Further studies to elucidate this problem are in progress.

Summary

The clinical findings in two allergic children with acute hemolytic episodes in association with asthma, allergic rhinitis or eczema have been described. The hemolytic reaction was found to be induced by the ingestion of minute amounts of foods or the inhalation of substances known to produce antigenic action in sensitized individuals.

The hematological findings in one of the children were consistent with a diagnosis of chronic acquired hemolytic anemia, which exacerbates when the patient is exposed to substances giving increased hemolytic rate.

It is suggested that some sort of allergic reaction is the cause of the abnormal hemolytic rate following the exposure. The similarity to favism has been discussed.

Episodes hémolytiques comme cause de l'ictère chez des enfants atteints d'une affection allergique: « Jaunisse allergique ».

Les recherches cliniques, exécutées chez 2 enfants allergiques avec des épisodes hémolytiques aiguës, associées à de l'asthme, de la rhinite allergique ou à de l'eczéma, ont été décrites. Il a été constaté que la réaction hémolytique est provoquée par l'ingestion de faibles quantités de nourriture, ou par l'inhalation de substances connues de manifester une action antigène sur des individus sensibilisés. Chez un des enfants, les recherches hémolytiques sont conformes au diagnostic d'une anémie hémolytique chronique non-congénitale, qui irrite lorsque le malade est exposé à ces substances provoquant une augmentation du taux hémolytique. Il a été suggéré qu'une quelconque sorte de réaction allergique est la cause du taux hémolytique anormale, se produisant à la suite de l'exposition. On a discuté la ressemblance au favisme.

Hämolytische Zwischenfälle als Ursache von Gelbsucht bei Kindern mit allergischer Krankheit. „Allergischer Icterus".

Die klinischen Befunde bei zwei allergischen Kindern mit akuten hämolytischen Episoden im Zusammenhang mit Asthma, allergischem Schnupfen und Ekzem werden beschrieben. Es wurde festgestellt, dass die hämolytische Reaktion von der Verdauung kleinster Mengen von Nährstoffen oder Einatmung von Substanzen, welche bekanntlich bei empfindlichen Individuen als Antigene wirken können, hervorgerufen worden war. Bei einem der Kinder waren die hämolytischen Symptome im Einklang mit der Diagnose einer chronischen erworbenen hämolytischen Anämie, welche, wenn der Kranke dem Einfluss dieser Substanzen, die Hämolyse in erhöhtem Grad bewirken, ausgesetzt wird, eine Verschlimmerung erfährt. Die Vermutung wird ausgesprochen, dass eine Art von allergischer Reaktion den abnormen hohen Grad der der Aussetzung folgenden Hämolyse bewirke. Die Ähnlichkeit mit Favismus wird erörtert.

Episodios hemolíticos determinantes de ictericia en niños alergicos. «Ictericia alergica».

Descripción de hallazgos clínicos en dos niños alérgicos afectos de episodios hemolíticos agudos asociados con asma, rinitis asmática o eczema. Se comprueba que la reacción hemolítica fué inducida por la ingestión de minimísimas cantidades de a-

mento o por la inhalación de sustancias conocidas por su acción antigénica, manifiesta en los individuos sensibilizados. En uno de los niños, los hallazgos hemolíticos fueron consistentes del diagnóstico de anemia crónica adquirida y exacerbada cuando el enfermo está expuesto a aquellas sustancias producentes de una proporción hemolítica creciente. Se sugiere la existencia de una reacción de índole alérgica como causa determinante de la proporción hemolítica anormal subsiguiente a la manifestación. Discusión de la semejanza con el favismo.

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Infectious Mononucleosis and Pseudomononucleosis in Childhood

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I. Infectious Mononucleosis

Until a specific micro-organism causing infectious mononucleosis has been identified, the diagnosis of this condition will depend entirely on the clinical picture.

The haematological findings, which have lent their name to the disease, are most valuable for a tentative diagnosis. In recent years, however, it has been stressed by many authors that mononuclear cells closely resembling those of infectious mononucleosis are found in many other states, especially such of viral origin (Leibowitz, and others). The terms "virocytes" or "stress cells" have been adopted. It should be emphasized that in these diseases of known origin, the number and polymorphism of abnormal cells rarely compares with that often found in infectious mononucleosis.

Other clinical signs of the disease, such as membranous tonsillitis, generalized enlargement of the lymph glands, splenomegaly, dysfunction of the liver, possibly also signs from the CNS, exanthema, puffiness of the eyelids, etc., are obviously not pathognomonic, even though they may support the diagnosis, especially if they appear in combination.

Of great importance is the appearance of heterophilic antibodies in the blood (Paul & Bunnell, 1932). With the introduction of the adsorption technique (Davidsohn, 1938), the specificity of the test has gained considerably, and a positive reaction must be interpreted as giving strong support to the diagnosis. Some authors, such as Hoagland (1952), are of the opinion that only those cases with a positive serum reaction should be accepted; others maintain the view that sero-negative cases of infectious mononucleosis do in fact occur (Leibowitz, 1956).

If the diagnosis of infectious mononucleosis is restricted to the sero-positive cases, the disease picture will show a more uniform clinical type. As an example may be mentioned the group of 56 adult cases observed by

Hoagland over a number of years at West Point. Of the total number, 78.6% had a pharyngeal, 19.6% a typhoidal, and 1.8% a gastrointestinal syndrome.

When assessing the Paul–Bunnell reaction it is necessary to bear in mind that it may sometimes become positive at a relatively late stage, and that the reaction may remain positive for a comparatively brief period only. It is therefore necessary to perform repeated tests before the reaction can be said with certainty to be negative. According to Bennike (1954) the average titre is lower in children below 15 years of age, and also remains positive for a shorter period than is the case in adults.

Contradictory to a statement by Hoagland (1955, p. 271) typical seropositive cases of infectious mononucleosis are not rare in childhood (Niggemeyer, Petrides, Gachet & Price, Szczepánska, and others). Two typical cases are now briefly reported.

Case 1.—L. H. A boy aged 7½ years. (Record number 962/54.)

Since September 22 there had been enlargement of the right submandibular glands, with slight pyrexia and weakness. On admission to hospital on Sept. 30 his general condition was good, he had sore throat and puffiness of the eye-lids. There was slight general lymphadenosis, with a large gland in the right submandibular region. The liver was palpable at the costal margin, and the spleen two finger-breadths below. During the first 3–4 days the boy was subfebrile, and then afebrile. Micro-sedimentation rate (MSR) 24-11. Sept. 30, leukocytes 13,600 (70% mononuclear, mostly atypical). Oct. 1, Paul-Bunnell 1/64 (specific). Oct. 7, Paul–Bunnell 1/128 (specific). Liver function tests normal. Oct. 13 he was discharged from hospital in good condition.

Case 2.—H.-E. H., a boy aged 7 years and 10 months. (Record number 345/55.)

Since March 15 he had had an enlarged gland in the neck and slight pyrexia. Increasing gland enlargement caused admission to hospital on March 29. He was in good general condition, but had slight conjunctivitis and puffiness of the eye-lids. The throat was sore and the lymph glands in all regions enlarged, in the left mandibular region reaching the size of a hazel nut. The liver was not palpable, but the spleen could be felt one finger-breadth below the costal margin. During the five days' stay in hospital the temperature remained at about 38°C. MSR 37-30. March 30, leukocytes 19,700 (79.5% mononuclears, most of them atypical). March 30, Paul-Bunnell 1/512 (specific).

In addition to these two serologically proved cases, another two cases in children of the same age will be described. The clinical picture was closely similar, but the Paul–Bunnell reaction was negative.

Case 3.—K. J., a girl aged 7 years and 7 months. (Record number 39/55.)

Since December 16, 1954, the patient had had an upper respiratory infection with sore throat, arthralgia, and a swinging temperature. From Dec. 19 there was increasing enlargement of the cervical glands. Penicillin treatment was without effect,

and the girl was therefore admitted to hospital on Jan. 3, 1955. Her general condition was good, she showed puffiness of the eyelids, follicular tonsillitis, and enlargement of the submandibular and cervical glands. The liver was palpable at the costal margin and the spleen one finger breadth below. Jan. 3, leukocytes 15,900 (67 % mononuclears, a large number of them atypical). Jan. 4, Paul–Bunnell negative. Jan. 12, Hanger +, Thymol 3.6 units, bilirubin 1.6 mg %. She became afebrile during her stay in hospital. MSR 34-42. She was discharged from hospital on Jan. 17 in good health.

CASE 4.—S. E., a girl aged 9½ years. (Record number 629/51.)

Since July 3 the patient had had a swinging temperature with peaks exceeding 40°C. Sulphonamides and penicillin were without effect. On July 16 the girl was admitted to hospital. The following day she had tonsillitis, the tonsils being partially coated. The cervical glands were enlarged. The spleen could be felt one finger-breadth below the costal margin, and was rather firm. Kernig 80°. During the first few days the temperature was 38–38.5°C, and then slowly subsided. MSR 33-34. July 18 leukocytes 14,500 (90 % mononuclear cells, many of these atypical). Paul–Bunnell negative on July 17 and July 25. Liver-function tests on July 17, bilirubin 1.5 mg %, alkaline phosphatase 17, Hanger + + +, thymol 6.4 units. July 25, bilirubin 0.9 mg %, alkaline phosphatase 14, Hanger + +, thymol 4.5 units. She was discharged on July 25 in good health.

In Case 3 the Paul–Bunnell reaction was tested only once, 19 days after the onset of disease. The possibility remains that a test taken at an earlier, or even at a later date might have been positive. In Case 4, two Paul–Bunnell reactions, taken 14 and 22 days after the onset of illness, were negative. With these findings the diagnosis of sero-negative infectious mononucleosis might seem attractive.

Positive Paul–Bunnell reactions have been reported as early as in the first year of life (e.g. Gachet & Prices, Leibowitz, Petrides), but only exceptionally have such reactions been obtained on adsorbed sera. In this connection it might be of interest to note that we have seen titers as high as 1/1024 which on adsorption proved to be non-specific. We have performed Paul–Bunnell reactions at the Paediatric Clinic of Uppsala in a comparatively large number of young children, but we have never obtained a positive reaction below 5 years of age.

II. The Influence of Age on the Outcome of the Paul–Bunnell Reaction

In order to obtain an idea of the age distribution of positive Paul–Bunnell reactions, and at the same time to test a possible correlation between age and intensity of the reaction, a large series of cases from the Hospital for Infectious Diseases in Stockholm was examined. This material includes all patients with positive reactions observed between 1951 and 1956. Reactions

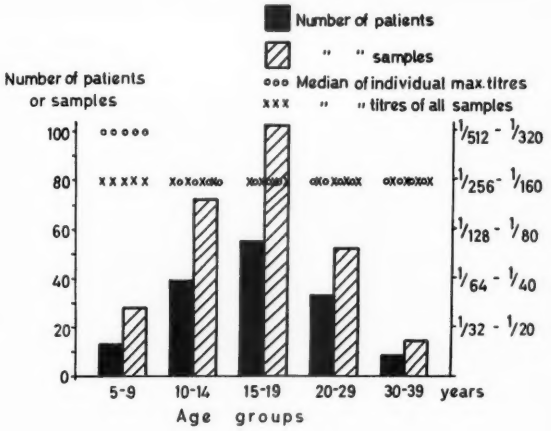

Fig. 1. The influence of age on the outcome of the Paul–Bunnell reaction. Age distribution of positive titres. Mean values for maximal titres in the various age groups.

exceeding 1/20 or 1/32 after adsorbtion were accepted as positive. In Fig. 1 the results are recorded in relation to the age of the patients. Not a single positive reaction was obtained before 5 years of age. In the age period 5–9 years positive reactions are already of common occurrence, and represent 8.8 % of the total, in the age period 10–14 years 26.4 % of the total.

In Fig. 1 also the intensity of the reactions is related to age. No interdependence could be demonstrated in this material.

The reason why positive Paul–Bunnell reactions are so rare during the first few years of life may be either a correspondingly low incidence of infection, or an age-specific lack of ability to form heterophile antibodies. Which of these alternatives is correct cannot yet be decided. It is a well known fact, however, that the capacity to form antibodies may be low in young children. This drawback is usually limited to the first 3–6 months of life, but the difference may sometimes persist over longer periods (Tunevall and others). To our knowledge there are no observations concerning the influence of age on the ability to form heterophile antibodies, for example, following the injection of heterologous serum.

It is therefore necessary to establish whether there do in fact appear during the first few years of life disease pictures which, with respect to their clinical findings, resemble the true infectious mononucleosis of older children and adults. Over a number of years one of us (B. V.) has devoted interest to this problem. It is undeniable that in children obscure disease pictures are not infrequently seen, characterized by fever, glandular enlargement, spleno-hepatomegaly, occasional conjunctivitis and exanthema, and a mononuclear leukocytosis with cells of virocyte type. Like some

other clinicians, we have noted that such disease pictures are prone to appear during the winter and that there is a tendency to periodic accumulation of cases.

III. Pseudomononucleosis

In 1889 Pfeiffer published a brief report of an epidemic of "Drüsenfieber", mainly afflicting children of school age. In the following years this concept aroused considerable interest and discussion. Some of the relevant papers date back to the first decades of this century. It is probable that with modern diagnostic methods many of the cases classified as "Drüsenfieber" could have been given a more precise diagnosis such as streptococcal adenitis, tularaemia, toxoplasmosis, or adeno-virus infection. Some of the epidemics described in the literature have shown such special features, however, that even to-day a disease *sui generis* must be seriously considered. This may be true of the cases originally described by Pfeiffer, the epidemic of "lymphaemoides Drüsenfieber" described by Glanzmann in Bern (1930), and also some others, where more complete clinical data are available (Petrides, Thomsen, and others). The opinion has been expressed that disease states of this kind might in fact be identical with infectious mononucleosis. The same idea has been put forward concerning certain other epidemics of febrile infection, in which glandular enlargement has been less conspicuous, but where the leukocyte picture has resembled that in infectious mononucleosis (e.g. Reyersbach & Lenert, 1941, and Goldthwait & Eliot, 1951). Several authors have been decidedly sceptical about such a view, and quite recently Hoagland (1955) has gone into some details of critical evaluation.

It is certainly true that one and the same type of infection may provoke several quite different clinical pictures (e.g. the virus of Coxsackie, Herpes simplex, adenovirus), but it would indeed be remarkable if the same organism could precipitate at one time an *epidemic*, in which all cases show a slight pharyngitis and glandular enlargement in the neck only (as in Pfeiffer's epidemic), and at another time *sporadic* cases of typical infectious mononucleosis with intense tonsillitis and generalized glandular enlargement. Any attempt to generalize about a possible identity of infectious mononucleosis with "Drüsenfieber" would seem futile, bearing in mind the heterogeneity of the latter both clinically and epidemiologically. Some epidemics, however, have shown many clinical features in common.

A few years ago one of us (Vahlquist, 1952) had the opportunity to observe in Uppsala a small epidemic of a disease which deserves the name "pseudomononucleosis". All the children afflicted were in the first few years of life. The dates and the age distributions of hospitalized cases com-

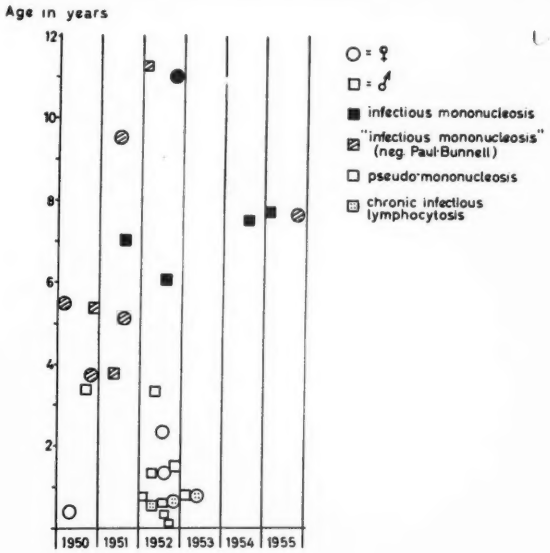

Fig. 2. The incidence in child in-patients of (1) infectious mononucleosis, (2) pseudo-monucleosis, and (3) chronic infectious lymphocytosis.

pared with cases of typical infectious mononucleosis are evident from Fig. 2. The maximum blood changes and certain other clinical data are shown in Table 1. Bone-marrow biopsy was performed only in a few cases: the findings were not specific. In addition to the cases admitted to hospital, many others were seen. The following serological tests were done in a number of cases: Paul–Bunnell, toxoplasmosis, Herpes simplex, and parotitis. Except for one case of suspect recent infection with Herpes simplex all others were negative.

Two typical histories (Cases 5 & 6) are summarized below.

Case 5.—S. P., a girl 5 months old. (Record number 495/50.)

The patient had a history of diarrhoea since May 1. She was admitted to hospital on May 6 in poor general condition and with signs of dehydration. Faeces culture: no pathogens. Following therapy she made rapid improvement. May 16, Widal neg. From June 2 she had slight pyrexia during one week (max. 38.2°C) and a maculopapular rash. At the same time there was slight pharyngitis and slight enlargement of the nuchal and cervical glands. The liver could be felt 1 finger-breadth below the costal margin, and a few days later the spleen was palpable 2 finger breadths below the costal margin. The splenomegaly subsequently rapidly subsided. June 9, leukocytes 19,500 (89 % mononuclear cells, some partially of the McKinley type). June 12, leukocytes 15 600 (81 % mononuclear cells, a few McKinley cells). June 15, leukocytes 7100 (81.5 % mononuclear cells, a few McKinley cells). June 7, Paul–Bunnell reaction negative, serum bilirubin 0.5 mg %, thymol 1.5 units, Takata negative. June 19, discharged from hospital in good health but still with slight lymphadenosis and slight

TABLE 1

Clinical signs and white blood picture in twelve cases of pseudomononucleosis.

Case history	Age yr.	Age mo.	Sex	Clinical signs: Pharyngitis	Lymphadenopathy	Enlarged liver	Enlarged spleen	Exanthema	White blood picture: Total white count	Stab %	Polymorphonucl. %	Eo %	Baso %	Mono %	Plasma %	Lymphocytes
S.P. 495/50		6	F	+	+	+	+	+	19,500	3.0	6.0	2.0	—	10.0	2.0	77.0
L.J. 1085/50	3	6	M	+	+	+	+	−	11,400	5.5	2.5	0.5	—	7.0	—	62.0
G.A. 75/52	1	6	M	+	+	+	+	−	8,600	1.5	—	1.5	1.5	2.0	—	92.5
P.C. 502/52	1	6	M	−	+	−	−	+	13,400	2.5	44.0	3.0	0.5	2.0	—	48.0
M.L. 563/52	3	6	M	+	+	−	+	+	17,400	1.5	19.0	1.0	—	3.0	—	75.5
B.E. 676/52	2	4	F	+	+	+	+	−	13,700	2.0	11.0	1.5	—	12.0	—	73.5
A.L. 714/52		4	M	−	+	+	+	−	9,200	0.5	23.5	2.0	—	6.0	—	68.0
R.L. 747/52		9	M	−	+	+	+	−	12,700	3.0	17.0	2.0	—	2.5	—	75.5
I.B. 759/52		2	M	+	−	+	−	−	13,600	0.5	8.5	5.0	—	9.0	—	77.0
E.P. 853/52	1	4	F	+	+	+	+	+	10,500	6.5	25.0	4.0	—	4.5	—	60.0
B.R. 965/52	1	6	M	+	+	+	+	+	8,100	0.5	19.0	—	—	9.0	1.5	70.0
L.F. 199/53		10	M	+	+	−	−	−	9,200	2.0	15.0	5.0	—	5.0	—	73.0

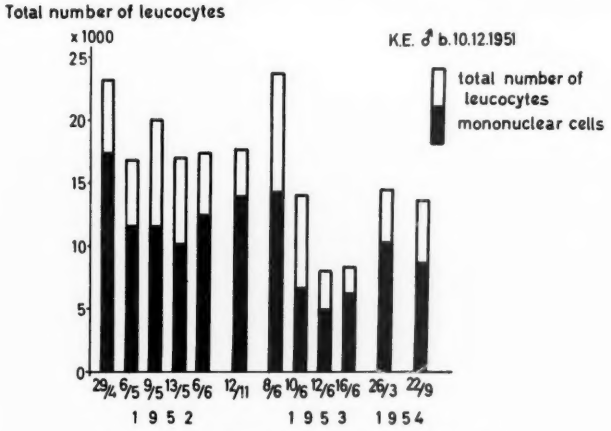

Fig. 3. Case 7, chronic infectious lymphocytosis.

spleno-hepatomegaly. July 25, the temperature was again 39°C, there was exanthema, dyspepsia, and splenomegaly 2 finger-breadths below the costal margin. July 26, 27,800 leukocytes (30 % mononuclear cells). Rapid convalescence ensued.

Case 6.—B. E., a girl aged 2 years and 4 months. (Record number 676/52.)

Since July 17 this child had been fretful and whining, with a temperature of 38–39.9°, but with no signs of infection. On July 22 she was admitted to hospital. Her general condition was good, but she had a slight pharyngitis, moderately enlarged tonsils, and slightly enlarged glands in the submandibular, cervical, and inguinal regions. The liver and spleen were palpable at the costal margin. On July 24 there were in addition follicular conjunctivitis, coating of the left tonsil, and increasing enlargement of the lymph glands and the spleen. July 22, leukocytes 7700 (88 % mononuclear cells). July 26, leukocytes 13,700 (85.5 % mononuclear cells with some atypical cells), MSR 30. July 29, Paul–Bunnell negative.

After the acute phase, many of the children manifested long persisting subfebrility, glandular enlargement, anorexia, and irritability. Blood tests revealed an increase in the number of lymphocytes, with virocytes, over many months. In a few cases pronounced lymphocytosis presisted for years, giving the picture of "chronic infectious lymphocytosis" described by Carl Smith in 1941.

Case 7.—K. E., a boy 6 months old. (Record number 441/52.)

On April 19th, dyspepsia was noted followed by slight pyrexia. On examination on April 29 he was found to have slight pharyngitis, with leukocytes 23,100 (68 % mononuclear cells). A tentative diagnosis of infectious lymphocytosis was made. Since fever continued, the boy was admitted to hospital on May 6. His general condition was good, the mucous membranes of the throat were pale, and the lymph glands and spleen were not enlarged. The bone marrow showed toxic granulations in the myeloid cells, but was otherwise normal. On May 11 there was slight pyrexia and slight generalized

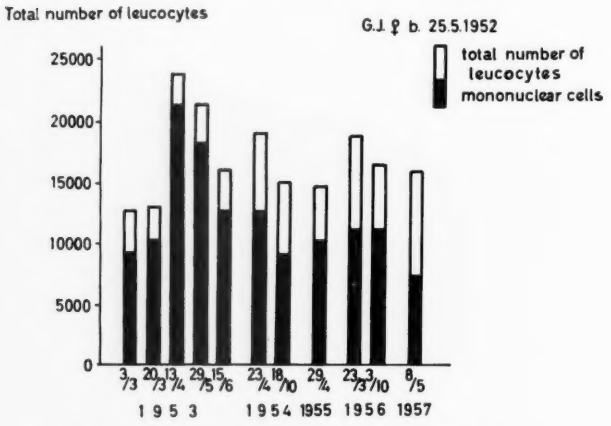

Fig. 4. Case 8, chronic infectious lymphocytosis.

lymphadenosis, with MSR 8-6. May 6, leukocytes 16,800 (69 % mononuclear cells), and the leukocytosis proved to be very persistent (Fig. 3). June 9, Paul–Bunnell reaction negative, tests for toxoplasmosis and herpes simplex negative. Periods of "weakness" and fretfulness appeared over many months but normal development took place. The blood picture was normal except for the leukocytosis.

CASE 8.—G. J., a girl aged 8 months. (Record number 136/53.) (Hospital for Infectious Diseases, Uppsala.)

On Feb. 9, the temperature was 39°C and vomiting took place pharyngitis was discovered and "Elkosin" was prescribed. After a period of slight pyrexia there was on Feb. 22 a further rise in temperature to 38.5°, and the child became fretful and irritated. She was admitted to hospital on March 2. She was pale and underweight, the throat was rough, and the cervical glands were moderately enlarged. The liver was palpable at the costal margin, the spleen could not be felt. Treatment was commenced with aureomycin. On March 4 increasing glandular enlargement became apparent, with hepatomegaly and fever. From March 7 the patient was afebrile, MSR 6. March 3, leukocytes 12,600 (72 % mononuclear cells, mostly atypical). On March 11 the patient was again in good general condition. The blood picture during the stay in hospital and at follow-up examinations during the subsequent years are shown in Fig. 4. The girl had a persistent tendency to slight febrile reactions and an increasing anorexia, but otherwise developed normally.

In spite of the fact that we have ever since been on the outlook for cases of this type, we have seen only a few in marked form. On the other hand, we have seen numerous children with pyrexia of uncertain origin, and with lymphocytosis including the appearance of many atypical cells in the peripheral blood. Such findings are hard to assess, however, during an age period when primary viral infections are probably more frequent than at any other time of life, and when there is a natural tendency to "lymphatic

reactions" (Finkelstein). In fact, Fichtelius & Vahlquist (1955) have demonstrated that apparently healthy children aged 1–3 years regularly show a considerable number of "atypical lymphocytes" in their blood, probably as the result of repeated subclinical infections.

The question may be raised of whether the "pseudomononucleosis" now described is identical with the true infectious mononucleosis seen in older children and adults. Until the aetiology of the conditions is clear it is impossible to answer this question. The consistently negative results of the Paul–Bunnell reactions and the absence of severe tonsillitis might be due to age-specific variations in reaction. Against the identity of the states, however, are not only the differences in epidemiology and clinical picture but also the fact that, although cases of mild disease with hematological changes are at time quite common, typical sero-positive cases of infectious mononucleosis are not at the same time found in higher than normal numbers.

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Summary

1. Infectious mononucleosis with a positive Paul–Bunnell reaction is extremely rare below 5 years of age.

2. The cases of infectious mononucleosis with positive Paul–Bunnell reaction which appear in increasing number from 5 years of age and onwards do not differ from adult cases with respect to intensity and duration of the serological reaction. Nevertheless it is possible that the marked rarity of positive Paul–Bunnell reactions below 5 years of age may be explained, at least in part, by a defect in the capacity of forming antibodies during this period.

3. Epidemic "Drüsenfieber" in children is a heterogeneous disease picture. Hence it is unwise to generalize on the identity or non-identity of this state with typical sero-positive cases of infectious mononucleosis.

4. A brief report is given of an epidemic of "pseudomononucleosis" in small children. The most marked clinical signs were fever, glandular enlargement, spleno-hepatomegaly, exanthema, and abnormalities of the leukocyte picture. Serological tests (Paul–Bunnell reaction, toxoplasmosis, herpes simplex, parotitis) were consistently negative, except in one case of recent probable Herpes simplex infection.

Mononucléose infectieuse et pseudo-mononucléose chez l'enfant.

Une mononucléose infectieuse avec une réaction de Paul-Bunnell positive est extrêmement rare chez les enfants de moins de 5 ans. Quant à l'intensité et la durée de la réaction sérologique, les cas d'une mononucléose infectieuse avec une réaction de Paul-Bunnell positive, se présentent plus fréquemment à partir de l'âge de 5 ans et plus tard, ne diffèrent pas de ceux ayant lieu à l'âge adulte. Néanmoins, il est possible que la rareté remarquable des réactions de Paul-Bunnell positives chez les enfants de moins de 5 ans puisse être expliquée, du moins partiellement, par une capacité défectueuse de la formation d'anticorps pendant cette période. La « Drüsenfieber » épidémique chez les enfants a un aspect clinique hétérogène. Il n'est donc pas raisonnable de généraliser en ce qui concerne l'identité ou la non-identité des cas typiquement séropositifs de mononucléose infectieuse, mentionnés dans ce comte-rendu. On donne un résumé sur une épidémie de « pseudo-mononucléose » chez de petits enfants. Les caractéristiques cliniques les plus remarquables étaient : une fièvre, une hypertrophie glandulaire, une hépatosplénomégalie, un exanthème et des anomalies dans l'aspect des leucocytes. Les tests sérologiques (réaction de Paul-Bunnell, toxoplasmose, herpès simple, parotidite) étaient, conformément à cela, négatifs, à l'exception d'un seul cas ou il s'agit probablement d'une infection d'herpès simple récente.

Infektiöse Mononukleose und Pseudomononukleose im Kindesalter.

Infektiöse Mononukleose mit positiver Paul-Bunnellschen Reaktion ist unter dem Alter von 5 Jahren ausserordentlich selten. Die Fälle von infektiöser Mononukleose mit positiver Paul-Bunnellschen Reaktion, welche in zunehmender Zahl von 5 Jahren aufwärts vorkommen, unterscheiden sich weder in Intensität noch in der Dauer der serologischen Reaktion von Fällen bei Erwachsenen. Nichtsdestoweniger ist es möglich, dass das auffallend seltene Vorkommen von positiven Paul-Bunnellschen Reaktionen unter dem Alter von 5 Jahren, zumindest teilweise durch einen Unfähigkeit, Antikörper in diesem Alter zu bilden, erklärt werden könnte. Epidemisches Drüsenfieber bei Kindern ist ein heterogenes Krankheitsbild. Daher ist es unweis, über die Identität oder Nicht-identität dieses Zustandes mit typischen sero-positiven Fällen infektiöser Mononukleose zu verallgemeinern. Ein kurzer Bericht über eine Epidemie von Pseudomononukleose bei kleinen Kindern wird erstattet. Die aufallendsten klinischen Zeichen waren Fieber, Vergrösserung der Lymphdrüsen, Spleno-hepatomegalie, Exanthem und Abnormalitäten im Leukozytenbild. Serologische Teste (Paul-Bunnellsche Reaktion, Toxoplasmose, Herpes simplex, Parotitis) waren beständig negativ, mit der Ausnahme eines Falles von frischer wahrscheinlichen Herpes simplex Infektion.

Mononucleosis infecciosa y seudomononucleosis infantiles.

La mononucleosis infecciosa de reacción Paul-Bunnell positiva, es rarísima antes de los 5 años de edad. Los casos de mononucleosis infecciosa de reacción Paul-Bunnell positiva, que aparecen en número creciente desde los 5 años de edad en adelante, no difieren de los casos adultos con respecto a la intensidad y duración de la reacción serológica. Sin embargo, es posible que la infrecuencia ostensible de reacciones Paul-Bunnell positivas antes de los 5 años de edad, pueda explicarse, por lo menos en parte, por un defecto de la facultad de formar anticuerpos durante ese período. La «Drüsenfieber» (fiebre ganglionar) epidémica infantil, tiene caracter patológico heterogéneo. Por consiguiente, no conviene generalizar la identidad o no-identificación de esta

condición, con casos típicos seropositivos de mononucleosis infecciosa. Se expone una breve relación de epidemia «seudomononucleosa» en niños pequeños. Los síntomas clínicos más salientes, fueron fiebre, ampliación glandular, esplenohepatomegalia, exantema y anomalías del cuadro leucocitario. Las pruebas serológicas (reacción Paul-Bunnell, toxoplasmosis, herpes simple y parotiditis), fueron consistentemente negativas, salvo en un caso de reciente infección probable de herpes simple.

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Early Diagnosis of Gonadal Dysgenesia (Turner's Syndrome)

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Chromosomal sex typing has helped to shed new light on Turner's syndrome. The method has also provided a possibility of establishing an early diagnosis.

Although earlier reports of the syndrome are available, Turner (1938) was the first to give a well defined description of the clinical picture in a presentation of 10 females above 15 years with infantilism, pterygium colli and cubitus valgus. The infantilism included stunted growth as well as lack of secondary sex characteristics. The triad infantilism, pterygium colli and cubitus valgus has since been known as Turner's syndrome and, with few exceptions, has been seen only in females. Independently of one another Varney, Kenyon & Koch (1942) claimed that hypogenesia or agenesia of the ovaries is the cause of sexual infantilism and not, as assumed by Turner, insufficiency of the hypophysis. These two groups based their assertion on the finding that the excretion of 17-ketosteroids and estrogens in the urine was decreased and that of gonadotrophins increased. Two of the patients were examined laparoscopically and no ovaries were seen in either. For a number of years the disease has also been known as ovarian agenesia. The above remarks apply to adult females and the clinical picture they show has been surveyed by Jackson (1953):

I. *Gonadal agenesia:*

(A) Primary: lack of ovarian development as proved by laparotomy.

(B) Secondary: primary amenorrhea, infantile uterus and vagina, mammary hypoplasia with pin-point nipples, and scanty pubic and axillary hair; normal or slightly retarded bone age with mild generalised osteoporosis; increased urinary gonadotrophins and frequently diminished urinary 17-ketosteroid excretion.

II. *Skeletal defects:* short stature with an adult height averaging about 55 inches, a "shieldlike" chest (broad and stocky with wide-spaced nipples), a span which is often wider than the height, a minor vertebral chondrodystrophy ("epiphysitis"); webbed neck and cubitus valgus are commonly but not invariably present.

III. *Associated anomalies*, which may include ocular defects such as squint, ptosis or cataract, cardiovascular defects such as coarctation of the aorta or hypertension independent of coarctation, mental retardation or deaf mutism.

The syndrome originally described by Turner has thus been extended to include other congenital malformations, not all of which need be present in every case. Only scanty literature is available on prepuberal cases. These patients are not old enough to show sex characteristics of any diagnostic value. Attempts have been made to confirm the diagnosis of ovarian agenesia before puberty by determination of the excretion of gonadotrophins in the urine. Thus, Crefeld & de Vaal (1949) and Kaijser (1949) described a girl aged 14 and 10, respectively, with increased excretion of gonadotrophins. Silver & Kempe (1953) also reported a 12-year-old and an 8-year-old girl with increased excretion of gonadotrophins and a third patient, aged 2 years and 9 months, who occasionally showed increased urinary gonadotrophins and in whom laparoscopy failed to reveal any ovaries. Wilkins (1950), however, claimed that an increased excretion of gonadotrophins is hardly likely before the age of 10–12 years, i.e. at the age the hypophysis is believed to start secreting this hormone. He described a 3-year-old girl of stunted growth with pterygium colli and coarctation of the sorta. Laparoscopy showed ovarian agenesia. Repeated gonadotrophin determinations from the age of 3 did not reveal any increased values until the child was 11 years old.

By a new method, cytologic determination of the sex-chromatin in certain tissue cells, it is often possible to make a diagnosis early in life, even at birth. The background of this method is as follows. The development of the gonads to ovaries or testes is determined by the chromosomal pattern. The further development of sex characteristics (in the rabbit) depends on the gonads and above all on the foetal secretion of the testes (Jost, 1947). On the nineteenth day of intra-uterine life of the rabbit the testes, but not the ovaries, begin to show signs of differentiation. The genital ducts, the urogenital sinus and external genitalia are at this time still in an indifferent stage. Jost's experiment (1947) showed that if rabbit foetuses of both sexes were castrated at that age, the genital system of both sexes then differentiated according to the female pattern. Castration at successively later stages resulted in a decreasing feminizing effect on the development of the genital system of the male foetuses, until finally castration no longer disturbed normal male sex development.

On the basis of Jost's experiments he (1950) as well as Wilkins (1950) assumed that an individual with Turner's syndrome might be a primary male lacking normal gonads at the moment decisive for further development, i.e. in man about the 9 weeks stage of foetal life. In 1949 Barr & Bertram

found a morphologically demonstrable sex difference in the nuclei of the nerve cells in cats. In female cells they found, in addition to the large nucleolus, a chromatin mass (sex chromatin) about 1 μ in diameter. A chromatin body of such size was seldom seen in nerve cell nuclei of male cats. Moore, Graham & Barr (1953) found similar sex differences in many cells in man. This provided a possibility of deciding the primary sex of the individual. On the basis of clinical observations Polani, Hunter & Lennox (1954) questioned the genetic sex of the individual with Turner's syndrome. They pointed out that coarctation of the aorta, which as an isolated defect is much more frequent in males than in females, is common in patients with Turner's syndrome. Thanks to the method of Moore *et al.* for determining the primary sex, they were also able to confirm that in three cases of Turner's syndrome with coarctation of the aorta, all 3 patients were genetically males. Since then 22 cases have been described by Grumbach, van Wyk & Wilkins (1955), in which 20 of the patients were of primary male sex; 4 cases by Décourt, Sasso, Chiorboli & Fernandes (1954), of whom 2 were primary male. By laparotomy and histologic examination of the gonads of some of these sextyped patients, it was discovered that what had formerly been interpreted as ovarian agenesia was in reality often testicular agenesia. On the basis of the finding of rudimentary medullary gonadal rests Grumbach *et al.* suggested that the term ovarian agenesia or gonadal agenesia should be replaced by the term gonadal dysgenesia.

In 1955 they pointed out the possibility of making an early diagnosis of Turner's syndrome by sex typing. By the finding of a male chromatin pattern on histologic examination of skin biopsy specimens they diagnosed the syndrome in 5 children of female outer appearance aged 2 months to 5½ years. Nelson (1956) accounted for 103 adults: 87 had a male and 16 a female chromatin pattern. This definitely described a large preponderance of primary male sex in Turner's syndrome (more than four-fifths) and thereby confirmed the diagnostic value of chromosomal sex typing. It is now possible to determine the sex with the same reliability in a more simple way by cytologic typing, a method which may be used routinely.

Methods

In our case chromosomal sex typing was done cytologically on the epithelium from oral scrapings according to Moore & Barr (1955) and on epithelial cells from urinary sediment according to Eskelund (1956). Instead of basic fuchsin according to Eskelund, in the present investigation cresyl echt violet was used with satisfactory results. As a comparison typing was also done on skin biopsy specimens by the method of Moore, Graham & Barr (1955).

All the methods permit a distinct differentiation between normal males and female.

Fig. 1 (*left*). Seven-year-old child of small stature (112 cm) with pterygium colli, broad chest, short fingers and toes.
Fig. 2 (*right*). Pterygium colli, oldish wizened face and low ears.

The specimens from oral cavity and urinary bladder can be collected with less inconvenience to the patient and place less requirements on the technical quality of the preparation and on the skill of the examiner.

The sex chromatin consists of a single plane convex body about 1 μ in diameter, lying inside the nucleus of the cell, usually against the membrane. "The evidence now available indicates that the sex-chromatin of female cells represents heteropycnotic portions of the two x-chromosomes that adhere to each other" (Plunkett & Barr, 1956).

In the case of Turner's syndrome described below, primary male sex and thus gonadal dysgenesia was diagnosed early by cytologic typing.

Case Report

K. O. (1281/56), born 18.9. 1949. The patient, aged 7, was admitted for investigation of systolic heart murmur.

Heredity.—The parents were healthy and of normal height. The father had a broad chest, short fingers and toe phalanges, a high palate and he was astigmatic. The

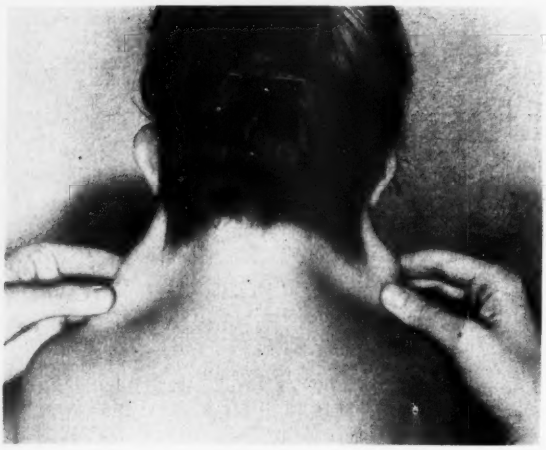

Fig. 3. Pterygium colli with low hair-line.

mother had a short and somewhat thick neck, with a low hair-line, but not pterygium colli. Otherwise no abnormalities were observed. No sterility or endocrine disturbances are known in the family. The father's maternal grandmother had low ears and a short neck, but not pterygium colli. Her siblings were all of short stature, 155–160 cm. Some features of her face resembled those of the patient's. The patient had two siblings: a 5-year-old brother of normal stature with short phalanges and a high palate but without other malformations; a 4-year-old sister of normal stature with a fairly broad chest and wide-spaced nipples.

History.—The mother had not had any known diseases during pregnancy, and delivery had been normal. Birth-weight 2900 g. Infancy was rather troublesome: the child tired rapidly and often vomited but never became cyanotic. Not until 6 weeks of age did the child reach birthweight. At birth and a week or so afterwards the patient had oedema of the dorsal surfaces of the hands and feet. The patient was cared for at the children's hospital from Oct. 26 until Nov. 19, for assumed cutis laxa.

The patient was at that time pale and tired and of oldish facial appearance. She was rather meagre, and turgor was decreased. The skin, especially that of the neck, could be lifted up in large folds. Physical examination of the heart revealed nothing of interest. Immediately after birth bilateral inguinal hernia were noticed: that of the left side disappeared spontaneously, that on the other side was surgically repaired in 1952. She was prone to catching cold, and she had otitis on several occasions. On routine medical examination at school in September 1956 a systolic heart murmur was discovered, for which the patient was referred to the Pediatric Clinic, Lund. No particular heart symptoms were noticed, but the parents reported that she could not run so quickly as her younger brother or sister. In addition she complained of cold feet.

On examination on Nov. 5, 1956, the child appeared healthy. She was 112 cm in height (average height of 7-year-old children in Sweden: 123 cm). Bodyweight 18.5 kg. The face was oldish and wizened, the ears and hairline in the neck were low, the sclerae were blue, the chest was "shieldlike" and the nipples were wide apart. She had cubitus valgus, pterygium colli, short finger and toe phalanges and a high palate (Figs. 1, 2 and 3). Heart: Systolic murmur with maximal intensity in the second left

intercostal space. The second aortic heart sound was accentuated. The blood pressure in the arms was 165/110, in the legs 105/80 mm Hg. The femoral pulse could not be felt. Roentgen examination of the heart, including heart catheterisation, gave the diagnosis of coarctation of the aorta with erosion of the ribs. Roentgen examination of the urinary tract and urography revealed nothing of interest. Skull X-ray was normal. Roentgen examination of the skeleton showed somewhat delayed development. Ophthalmologic examination: arteries in the fundus were somewhat narrow and markedly tortuous. No hemorrhages.

Laboratory studies.—K/serum 5.1 mEq/100 ml. Na/serum 143 mEq/100 ml. Chloride/serum 391 mg/100 ml, bicarbonate/serum 26.2 mg/100 ml. Urine: 17-ketosteroids 1.8 mg/100 ml. Gonadotrophins < 10 M.U./lit. Chromosomal sex typing: all of the samples examined from the patient gave unequivocal results—chromatin-negative cells, i.e. male chromatin pattern (Figs. 4–8).

Discussion

The patient was thus a child, aged 7, of stunted growth and external female appearance with pterygium colli, cubitus valgus, coarctatio aortae, low ears and low posterior hair line margin, a high palate and short phalanges. Such a clinical picture, often described in children, has been called status Bonnevie-Ullrich bilateralis in European literature since 1930. The genital sphere has received less attention. After perusal of the American literature of which he had not been aware earlier, Ullrich (1950) claimed that Bonnevie-Ullrich syndrome is identical with Turner's. Also other authors (E. K. Turner, 1954; Obermann, 1955) made the diagnosis of Turner's syndrome already in childhood simply on the basis of the external habitus of the patient, which they considered sufficient to predict a later absence of puberty. This conception must, however, be wrong because Rossi & Caflisch (1951) reported such habitus in both males and females: in some of them laparotomy revealed normal gonads and some afterwards had children. In addition Russel, Levin & France (1955) reported on a 12½ year old girl described one year earlier as a typical case of Turner's syndrome. Laparotomy, however, showed ovaries bilaterally, each with several follicle cysts.

On the other hand, it is known that cases of gonadal dysgenesia exist in which one or more of the malformations regarded as classical of Turner's syndrome, e.g. pterygium colli, infantilism or cubitus valgus, are missing. Thus retarded growth might be the only manifestation of gonadal dysgenesia (Grumbach *et al.*); therefore the genetic sex should be determined in all female cases of retarded growth of unknown origin. In both the polysymptomatic and the oligosymptomatic cases, establishment of a diagnosis of Turner's syndrome in children requires the demonstration of gonadal dysgenesia. The demonstration of such dysgenesia is of prognostic and

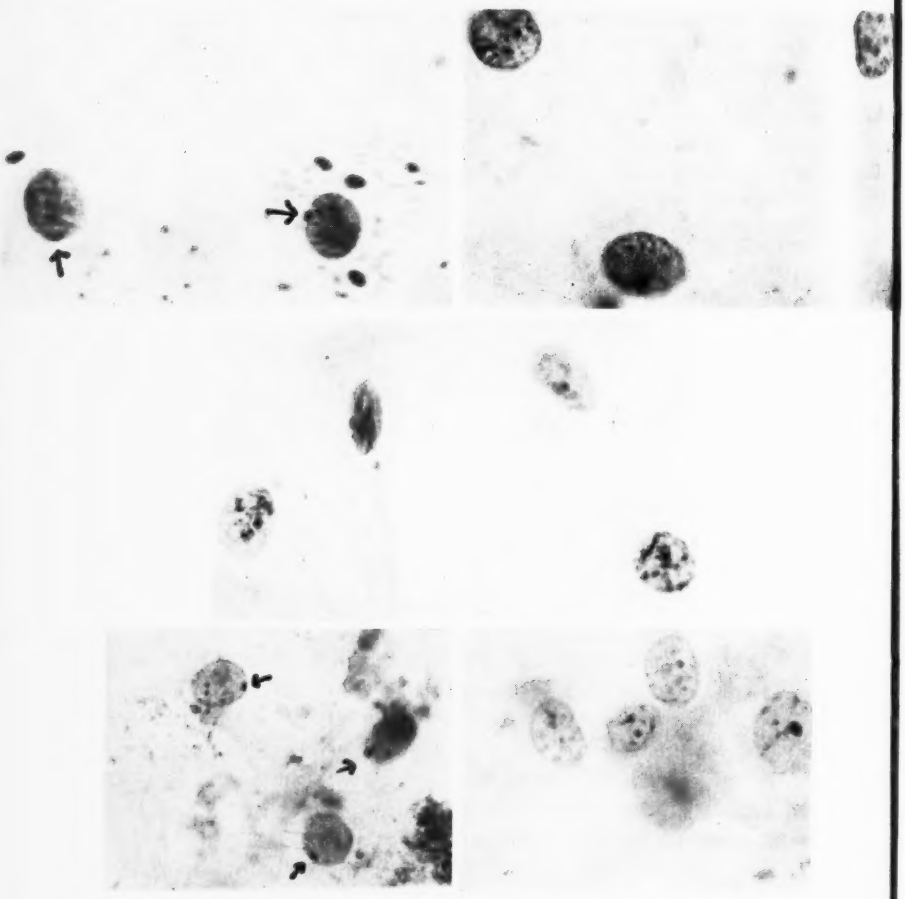

Fig. 4 (*top left*). Epithelial nuclei from oral mucosa of normal female. Sex-chromatin is marked with an arrow. × 880.
Fig. 5 (*top right*). Epithelial nuclei from oral mucosa of normal male. Sex-chromatin is lacking. × 880.
Fig. 6. Epithelial nuclei from patient's oral mucosa. Sex-chromatin is lacking. × 880.
Fig. 7 (*bottom left*). Epithelial nuclei from urinary bladder of normal female. Sex-chromatin is marked with an arrow. × 880.
Fig. 8. (*bottom right*). Epithelial nuclei from patient's urinary bladder. Sex-chromatin is lacking. × 880.

therapeutic importance, while most other symptoms are of subordinate interest. In about four–fifths of the cases, i.e. the primary male, the diagnosis can be verified by the finding of male chromatin pattern. The finding of a female pattern does not exclude the diagnosis.

Gonadal dysgenesia can also be regarded as the most extreme variant of male intersex. Transient forms with both female and male external features may also occur. "Male Turner's syndrome" (Avin, 1956) may be regarded as a special variant. The experimental background of these forms was given by Jost (1947), who got their counterparts by castrating male rabbit foetuses at successively later stages. Some of these variants may be difficult to distinguish from female intersex. This implies a widening of the range of indications for sex typing.

The genesis of the syndrome is obscure. Both environmental and hereditary factors have been discussed. To lead to gonadal dysgenesia the normal development of the gonads should—judging by Jost's experiment—be influenced during the first 8–9 weeks of foetal life. Exogenic injury during this time may give rise to varying malformations in any organic system (Warkany, 1947). The varying combination of malformations in Turner's syndrome can thus be explained by exogenic damage during the first 8–9 weeks of foetal life. On the other hand, an abnormal gene can give rise to several malformations in varying combinations. The coincidence of several abnormal genes can, of course, also lead to a polymorphous picture. Rossi & Caflisch, for example, believe the syndrome to be of genetic origin, while Grumbach *et al.* are more inclined to ascribe it to exogenic factors.

As to therapy might be mentioned that estrogen and subsequent estrogen-progesterone cyclically administered at the time of normal puberty can lead to development of the breasts and genitalia and even produce regular menstruations. Such medication has, however, little effect on growth of stature.

These patients believe themselves to be females. It may therefore be concluded that neither the sex chromosomes nor the hormonal substance has any decisive effect on psychosexual behaviour. There is no reason to inform the patient or the relatives of the primary sex.

Summary

With reference to the primary definition of Turner's syndrome an account is given of the extended picture of the syndrome. Special attention is given to the sexual infantilism, which was originally believed to be an ovarian agenesia but which is now ascribed to gonadal dysgenesia. Cytologic determination of the sex chromatin, a method developed in recent years, has become a valuable adjuvant in the establishment of a definite prepuberal diagnosis of gonadal dysgenesia. A report is given of a 7-year-old patient with Turner's syndrome including aortic coarctation. By cytologic determination it was found that the patient was of primarily male sex. The cytologic examination is illustrated. The underlying mechanism and the polymorphous picture in Turner's syndrome is discussed. It is concluded that gonadal dysgenesia must be demonstrated before a diagnosis of Turner's syndrome can be established in children.

Diagnostic précoce d'une dysgénésie des gonades (Syndrome de Turner).

A propos de la définition primaire du syndrome de Turner, on présente un compte-rendu de l'aspect étendu du syndrome. On a apporté en particulier attention à l'infantilisme sexuel dont on a supposé à l'origine que celui-ci était la conséquence d'une agénésie ovarienne, mais qui est actuellement attribué à une dysgénésie des gonades. Le dosage cytologique de la chromatine du sexe — une méthode développée ces dernières années — est devenue un adjuvant précieux pour établir un diagnostic prépubère définitif de la dysgénésie des gonades. On rapporte le cas d'un malade de 7 ans, atteint du syndrome de Turner, y compris une constriction de l'aorte. A l'aide du dosage cytologique, on a constaté que le malade était d'origine du sexe masculin. L'examen cytologique est illustré. Le mécanisme sous-jacent et l'aspect polymorphe dans le syndrome de Turner sont discutés. Il a été conclu qu'une dysgénésie des gonades doit être démontrée avant que l'on puisse diagnostiquer le syndrome de Turner chez l'enfant.

Frühdiagnose der Gonadendysgenesie (Turnersches Syndrom).

Unter Bezugnahme auf die primäre Definition von Turners Syndrom wird ein Bericht über das erweiterte Bild dieses Symptomenkomplexes angegeben. Besondere Beachtung wird dem sexuellen Infantilismus gewidmet, welcher ursprünglich als Ovarialagenesie aufgefasst worden war, aber jetzt einer Gonadendysgenesie zugeschrieben wird. Cytologische Bestimmung des Geschlechtchromatins, eine in den letzteren Jahren entwickelte Methode, ist zu einem wertvollen Hilfsmittel zur Festlegung einer entschiedenen Diagnose von Gonadendysgenesie vor Eintritt der Pubertät geworden. Ein Bericht über einen 7-jährigen Kranken mit Turnerschen Syndrom einschliesslich Aortenkoarktation wird vorgelegt. Mit Hilfe cytologischer Bestimmungsverfahren wurde gefunden, dass der Kranke in erster Linie männlichen Geschlechts war. Die cytologische Untersuchung wird erläutert. Der zugrundeliegende Mechanismus und das vielgestaltige Bild des Turnerschen Syndroms werden erörtert. Abschliessend wird gefordert, dass Gonadendysgenesie vorerst nachgewiesen werden muss, bevor eine Diagnose von Turnerschem Syndrom bei Kindern festgestellt werden kann.

Diagnóstico precoz de la disgenesia gonadal (Síndrome de Turner).

Con referencia a la definición primaria del síndrome de Turner, se expone un cuadro extensivo del mismo. Se dedica especial atención al infantilismo sexual, atribuído, en un principio, a agenesia ovárica, y, actualmente, a disgenesia gonadal. La determinación citológica de la cromatina sexual, método desarrollado en años recientes, se ha convertido en un valioso auxiliar para el establecimiento del diagnóstico prepubescente definitivo de disgenesia gonadal. Casuística de un paciente de 7 años de edad, presentando el síndrome de Turner, incluyendo coarctación aórtica. Por la determinación citológica, se comprobó que el paciente pertenecía primariamente al sexo masculino. Se da cuenta del examen citológico. Discusión del síndrome de Turner en relación con su mecanismo subyacente y cuadro polimorfo. Conclusión; Antes de establecer el diagnóstico de síndrome de Turner, en los niños, debe demostrarse la disgenesia gonadal.

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Ellis–Van Creveld Syndrome

Report of Two Cases in Siblings

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Ellis & Van Creveld, in 1940 (1), using a case previously reported by Holt & McIntosh (2) and two cases of their own, described the syndrome of chondrodysplasia, hydrotic ectodermal dysplasia, polydactylism, and congenital heart disease, the latter defect occurring in two of the three cases. Following the initial description, nothing concerning this syndrome appeared in the medical literature until 1951 when Weller (3), in a case report, described distal interphalangeal arthrogryposis as a part of the syndrome. The following year Caffey (4) gave a follow-up report on the case of Holt and McIntosh, presented two new cases, and made important observations on the roentgen appearance in the condition. In the same year Debré *et al.* (5) presented the first case on which an autopsy was performed. The pathological picture in the bones differed from that in achrondroplasia in that the rows of columnar cartilage maintained their parallel arrangements although the general picture was disorderly. The cardiac anomaly was shown to be an interventricular septal defect with an associated high interauricular septal defect. Other anomalies which were found included clubfeet, cleft palate, exophthalmos, and pathological thickening of the media of arterioles in the bone marrow. Chauss (6) has reported an autopsied case with cor triloculare biatriatum. Cases described by Gatto (7), Keizer & Schilder (8), Gallagher, MacGregor & Isrealski (9), Niemann, Stehlin & Manciaux (10), and Weiss & Crossett (11) bring the total number of reported cases to thirteen. These later cases added other rare findings such as sexual infantilism, hypospadias, hepatosplenomegaly, and a slate colored ring about the lacrimal caruncle of the eye.

The following examples of this syndrome are the first described in siblings.

Case Reports

Case 1

A three years and eight months old white female was referred to the University of Virginia Hospital for definitive diagnosis of recently discovered congenital heart disease. The heart murmur had first become apparent during a typical episode of acute congestive heart failure which followed a sore throat. She had previously exhibited no recognizable signs or symptoms of heart disease.

A review of systems did not demonstrate any symptoms except those of the present illness (congestive heart failure). The child, the product of a normal nine months gestation and uncomplicated labor and delivery, weighed 4330 g at birth. Significant in the past medical history was the amputation of at least one supernumerary digit from the medial aspect of each hand and foot.

In the family history it was learned that consanguinity existed. The paternal and maternal lines were interrelated in the ascending fourth generation where there had been a common ancestor. The patient's mother had had one pregnancy which was terminated by spontaneous abortion. The fetus, a male, appeared normal. Another infant, a female, died at the age of eight days and was said to have been blue from birth; there were extra digits present on both hands. An autopsy was not done. There were two other children, a normal male and a female who is described in Case 2.

The patient had held her head up from the prone position at three months, sat alone at seven months, crawled at nine months, stood at fifteen months, and walked at seventeen months. A single central incisor had been present at birth but for maternal comfort had been extracted shortly after birth. Further dentition was delayed until one year of age when the molars began to erupt and were followed by the appearance of the incisor and canine teeth.

The patient was an alert, cooperative, talkative, and intelligent little girl who did not appear ill. She was small in stature with a striking knock-knee deformity (Fig. 1). The temperature was 37.4 degrees centigrade, the pulse 130 per minute, respirations 26 per minute, and the blood pressure 90/65 mm of mercury. The upper lower ratio was 1.56.

The head was slightly elongated in the anteroposterior diameter. An internal strabismus of the left eye was present. The sulcus between the upper lip and gum was more shallow than usual, and the upper lip was smaller than normal giving the appearance of a lip following cheiloplasty. The mid-portion of the lip appeared to be underdeveloped. The teeth were small, variously shaped, and growing at irregular angles. There were seven upper and seven lower teeth present. The deciduous molar teeth were recognizable but it was difficult to determine which of the central teeth were missing because of the dysplasia of these teeth. The enamel was defective and numerous foci of caries were present.

There was a slight bulge to the left chest over the precordium. The apical thrust was in the left fifth intercostal space outside the midclavicular line and the cardiac dullness was percussed in the sixth intercostal space in the anterior axillary line. No thrills were palpated. There was a short, not particularly loud, coarse, systolic murmur along the left sternal border maximal at the base of the heart. A mid-diastolic murmur was heard just mesiad to the apex of the heart. The pulmonary second sound was split and not accentuated. The first sound was normal. The peripheral pulses were full and equal.

A soft, round, non-tender liver edge was felt five centimeters below the right costal

Fig. 1. Case 1 (*left*) showing internal strabismus, pseudohairlip, genu valgum, and short stature. Case 2 (*right*) is similar in appearance.

margin. The skin was faintly hyperpigmented and scalp hair was sparse in its distribution. The nails were variously shaped, small, thickened distally, convex in shape, and bore longitudinal ridges. There was marked angulation of the nail growth and several nails were rudimentary. The upper extremities appeared short and the fingers were quite short and broad. Scars were present on the ulnar aspects of both hands. The lower extremities were short and moderately severe genu valgum deformity was present. The toes were short and there was syndactylism of the first and second toes of the left foot. Scars were present bilaterally on the lateral aspects of the distal portions of the feet.

Routine examinations of the urine and stool were normal. The hemoglobin, white blood cell count, and differential white blood cell count were also normal. The serum electrolyte values and tests of liver function resulted in normal findings. An Old Tuberculin 1:1000 and a Wasserman test were negative. Fasting blood sugar, serum cholesterol, serum calcium, phosphorus, and alkaline phosphatase were all normal. The sweat chloride was 112 meq/l and the sweat sodium 21.0 meq/l. Paper electrophoresis of the blood serum showed the gamma globulin elevated (22.2 per cent with

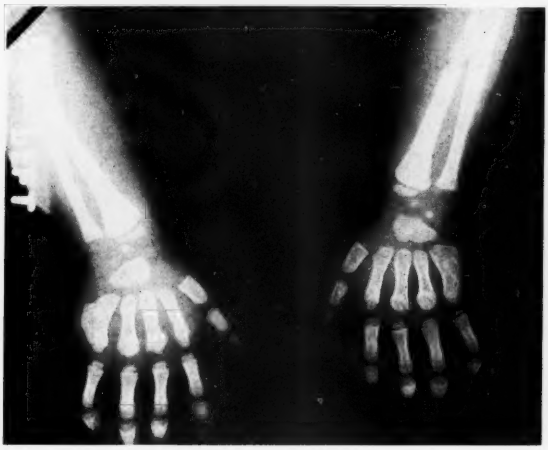

Fig. 2. X-ray of the hands of Case 1 showing changes in ossification centers, synmetacarpalism and syncarpalism.

a control value of 14.4 per cent) at the expense of the albumin fraction. The blood type was A, RH positive.

In the electrocardiogram an S_1, S_2, S_3 pattern was present in the standard limb leads, and right ventricular hypertrophy and incomplete right bundle branch block were also demonstrated. The fluoroscopic examination showed the pulmonary vascular bed to be normal and right ventricular hypertrophy to be present. Cardiac catheterization showed right and left superior venae cavae and an auricular septal defect which was thought to be a septum primum type.

Roentgenographic studies (Fig. 2) demonstrated progressive distal shortening of all bones of the extremities and medial curving of the humeri with flaring of the distal ends. The proximal ends of the ulnae and distal ends of the radii were also flared. Retardation of ossification in the primary centers and acceleration of ossification in the ossification centers of many of the metacarpal bones and phalanges were found. Fusion of the capitate and hamate bones was present bilaterally and there was bilateral synmetacarpalism of the fifth metacarpal bone with an anomalous sixth metacarpal bone. This bony fusion was more pronounced on the right. Genu valgum deformity of the legs was present and changes in the phalanges of the feet and metatarsal bones were similar to those changes described in the hand, but bony syndactylism was not found. Dentition was delayed. The skull, lung fields, and spine were normal.

While in the hospital, the patient was continued on digitalis, given mercurial diuretics, and maintained on a restricted salt diet for control of her congestive heart failure. The clinical findings and results of the various cardiac diagnostic tests were felt to be consistent with a diagnosis of a septum primum defect. The parents of the patient were instructed to continue giving the child digitalis, to have her followed for her heart disease, and to have her evaluated later concerning the need for orthopedic treatment.

Case 2

The second patient (Fig. 1) was a five-year-old white female and sister to Case 1. According to the parents she had been quite well all of her life and a general review of

Fig. 3. X-ray of the arms and hands of Case 2 demonstrating medial curving of the humeri, flaring of the distal ends of the long bones, progressive distalward shortening of the bones, polydactylism, syncarpalism, and changes in the ossification centers.

Fig. 4. X-ray of the legs of Case 2 showing genu valgum deformity, peaking of the proximal tibial head, and medial tibial exostoses.

systems failed to uncover any significant symptoms or signs except progressive genu valgum which had its onset when the patient commenced to walk. The past medical and dietary histories were normal, and the developmental pattern was slightly accelerated. Dentition had been delayed until one year of age when the deciduous molar teeth began to erupt, followed by the appearance of the canine and incisor teeth.

The patient's general demeanor was that of an alert, intelligent, cooperative little girl. She had a severe degree of genu valgum and her stature was small because of the short extremities. The temperature was 37.2 degrees centigrade, pulse rate 120 per minute, respirations 24 per minute, and blood pressure 110/60 millimeters of mercury. The upper lower ratio of the child was 1.47. There was a slight left internal squint. Her teeth were poorly developed and were irregular in shape; they were angulated in their growth from the gums and covered by defective enamel. The skin was faintly hyperpigmented. The nails were small and several were missing. There was pronounced angulation of growth of the nails from the nailbeds. The nails were of convex shape, longitudinally ridged, and thickened distally. The upper extremities were short, and the hands and fingers were short and broad. There was an accessory finger present on the ulnar side of each hand. Arthrogryposis was absent.

Inspection and auscultation of the chest failed to demonstrate abnormalities. There were no thrills. The apical thrust was in the fifth left intercostal space in the mi-

Fig. 5. Epiphysical plate (× 28) of the amputated accessory digit from Case 2 demonstrating the abortive columnar arrangements of cartilage cells and reduced capillary invasion into the cartilagenous plate.

clavicular line. The cardiac sounds were clear and the second pulmonic sound was split and louder than the second aortic sound. There was a soft, Grade I, systolic murmur of vibrating quality present about two centimeters from the left sternal border. The murmur was loudest in the second left intercostal space and was heard with diminishing intensity over the precordium and did not radiate outside of the cardiac limits. The remainder of the physical examination was normal.

Routine urine, stool, and blood counts were normal. The same studies performed in Case 1 were done on this patient and all of the results, including paper electrophoresis, fell within the normal range. The patient's blood type was A, Rh positive.

Roentgen examination (Figs. 3 and 4) showed the skull to be brachicephalic with a normal mandible and delayed dentition. There was progressive distalward shortening of all the bones of the extremities. Medial curving of the humeri was found and the radii and ulnae were normal. The capitate and hamate bones were fused bilaterally and a sixth digit was present on the ulnar side of each hand. Synmetacarpalism was not demonstrated. The metacarpal and phalangeal bones had delayed ossification in the primary centers and accelerated ossification of the secondary centers. There was a severe genu valgum deformity and exostoses on the medial aspects of the tibiae bilaterally. Peaking of the proximal heads of the tibiae was demonstrated and did not seem to be the result of pressure but was similar to those findings described by Caffey (4). The X-rays of the chest, heart and spine were normal.

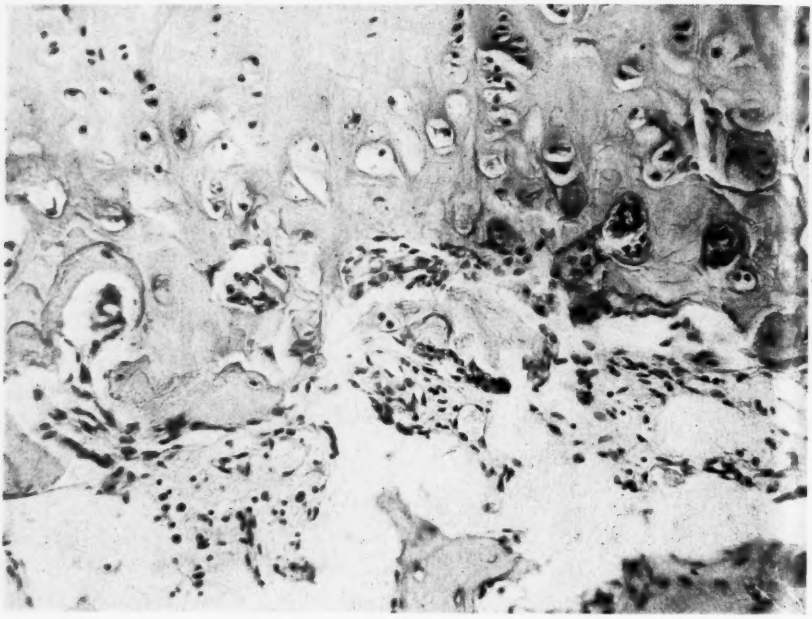

Fig. 6. Magnification × 90 of Fig. 5.

The hospital stay was uncomplicated. From the clinical findings, normal fluoroscopic examination and electrocardiogram, a diagnosis of innocent heart murmur was made; additional studies seemed unnecessary pending reevaluation. The patient was readmitted to the hospital in December 1956 for amputation of an extra digit and a unilateral osteotomy for her genu valgum deformity.

The gross examination of the disarticulated finger showed normal appearing skin but absence of the nail and nailbed. By microscopic examination (Figs. 5 and 6) the proximal interphalangeal space was lined by a synovial membrane but was narrowed by ingrowth of fibrous tissue. There was a decreased number of cartilage cells in the cartilagenous plate and those present showed an abortive columnar arrangement. The epiphyseal line was irregular and showed reduced and irregular capillary invasion of the cartilagenous plate. Osteoblasts were present and active but reduced in number.

It should be remembered that the pathological picture in this extra digit may be affected by lack of use and poor blood supply, the extent of which is unknown. Because of these factors this description does not necessarily represent the true pathological picture. However, since this picture closely parallels that described by Debré *et al.* (5), we feel that these findings are probably representative of the bony changes occurring in this syndrome.

Discussion

As described at present, the Ellis–Van Creveld syndrome consists primarily of chondrodysplasia, hydrotic ectodermal dysplasia, ulnar poly-

dactylism, and congenital heart disease. Less constant findings are distal interphalangeal arthrogryposis, a variety of bone defects, and other previously mentioned rare findings.

Grossly the chondrydysplasia is characterized by dwarfism due to shortening of the extremities so that the increased length of the trunk is more apparent than real. There may be deformities of the extremities such as genu valgum, curving in of the humeri, and other changes in bone shape. Polydactylism is characteristically seen on the ulnar side of the hand.

The X-ray findings described by Caffey (4) include progressive distalward shortening of all of the bones of the extremities, flaring of the proximal ends of the tibiae with lengthening of the lateral slope of the tibiae, polymetacarpalism, synmetacarpalism, syncarpalism, and changes in the ossification centers of the phalanges. Less constantly one may find similar changes in the bones of the feet, exostoses of the long bones, and dislocations of the heads of the radii.

Ectodermal dysplasia is manifested by defects of the teeth, nails and hair. The teeth are irregularly spaced, variously shaped, and imperfectly formed. Dentition is delayed. The nails have severe angulation of growth, distal thickening, longitudinal ridges, and may be entirely absent. Less constantly one finds partial alopecia and obliteration of the sulcus between the upper lip and gum. Other defects in the skin appendages have not been observed.

Including the present cases, congenital heart disease has been described in eleven of the fifteen reported cases. Except for the cases of Debré *et al.* (5) and Chauss (6) and Case 1 of the present report the heart lesions have been inadequately studied and no generalizations can be made concerning the type of lesion to be expected in future cases.

The two children presented in this report represent true cases of the syndrome described by Ellis & Van Creveld (1). This is the first incidence in which this syndrome has been described in siblings. Case 1 is a typical picture of the condition while Case 2, although complete in most of the major manifestations of the syndrome, lacks synmetacarpalism and the findings compatible with a diagnosis of congenital heart disease.

It has been previously mentioned that the sweat mechanism of affected persons has appeared grossly normal. Both of these patients exhibited normal sweat responses, and sweat electrolytes were within normal limits. The finding of hypergammaglobulinemia in Case 1 is not fully understood but it is felt that this elevation may represent an antibody response to the throat infection which preceded the onset of congestive heart failure.

In both of these cases, but more prominently in Case 1, the midportion of the upper lip was underdeveloped giving the pseudohairlip appearance

described by Weller (3). It would appear that the occurrence of internal squint (in our two cases and possibly in two other cases as evidenced by photographs in the papers of Ellis & Van Creveld (1) and Gatto (7)) is more frequent than one would expect by chance alone in so small a group of patients. The roentgenographic demonstration of acceleration of the primary centers and delay in the secondary ossification centers of the metacarpal bones has not been previously described and may constitute a further extension of the changes previously described by Caffey (4). The findings probably represent additional but less common examples of mesodermal dysplasia.

Ellis & Van Creveld felt that the syndrome was familial and was probably transmitted by a recessive gene. Consanguinity in four of the previous cases has given support to this concept. The findings of this report, that of two children and possibly a third child of consanguineous marriage, appear to be in agreement with the above impression, but the observed cases are insufficient in number to establish the exact mechanism of inheritance.

It is our opinion that the present name of chondroectodermal dysplasia is misleading. Such a name focuses attention on the defect of bone, teeth, and nails while giving no indication of the widespread involvement of all mesodermal derivatives. In order to place emphasis on the most widely affected germ layer, it is suggested that a more appropriate name would be ecto-mesodermal dysplasia.

Summary

1. Two cases of the Ellis–Van Creveld syndrome are presented. These are the first cases reported in siblings.

2. It is suggested that strabismus, pseudo-hairlip, and changes in metacarpal ossification centers are additional, though less frequent components of the syndrome.

3. Ecto-mesodermal dysplasia is proposed as a more descriptive name for this syndrome.

Le syndrome d'Ellis-Van Creveld. Rapport sur deux cas chez des enfants de mêmes parents.

Présentation de deux cas de syndrome d'Ellis-Van Creveld. Ce sont les deux premiers cas rapportés sur des enfants de mêmes parents. Il a été supposé que le strabisme, le pseudo bec-de-lièvre et les changements dans les centres de l'ossification métacarpienne sont des composants supplémentaires du syndrome, bien qu'ils soient moins fréquents. On a proposé d'appeler ce syndrome : dysplasie de l'ecto-mésoderme, étant un mot plus descriptif.

Das Ellis-Van Creveldsche Syndrom. Bericht über zwei Fälle bei Geschwistern.

Zwei Fälle von Ellis-Van Creveldschem Syndrom werden beschrieben. Diese sind die ersten bei Geschwistern, über die berichtet wird. Die Ansicht wird ausgesprochen,

dass Strabismus, Pseudohasenscharte und Veränderungen in metakarpalen Ossifikationszentren zusätzliche, wenn auch weniger häufige Bestandteile des Syndroms sind. Ekto-mesodermale Dysplasie wird als ein, dieses Syndrom besser beschreibender Name, vorgeschlagen.

Casuistica del síndrome de Ellis-Van Creveld en dos descendientes directos.

Se exponen dos casos de síndrome de Ellis-Van Creveld. Son éstos los primeros registrados en descendientes directos. Se sugiere que el estrabismo, el seudo labio leporino y los cambios en los centros de osificación metacarpiana, son constitutivos adicionales de este síndrome, aunque menos frecuentes. Se propone para este síndrome el nombre más descriptivo de displasia ectomesoderma.

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Spontaneous Histamine Shocks in Urticaria Pigmentosa[1]

by G. BLOOM, H. DUNÉR, B. PERNOW, J. WINBERG and R. ZETTERSTRÖM[2]

Since Unna in 1896 gave the original histological description of urticaria pigmentosa and characterized the skin changes as subepithelial accumulations of mast cells, the disorder usually has been looked upon as a benign disease of the skin. It seems necessary, however, to revise this opinion since in recent years several reports of urticaria pigmentosa associated with involvement of different internal organs have been reported (cf. Sagher & Schorr; Sagher; Asboe-Hansen & Kaalund-Jörgensen). In some instances even generalized mast cell leukemia simulating urticaria pigmentosa has developed (Sagher; Waters & Lacson). However, it is not only systemic involvement that threatens these patients. Hemorrhagic disorders have repeatedly been described (Asboe-Hansen, 1950a; Waters *et al.*), causing a fatal outcome in at least one patient (Gardner & Tice).

The purpose of this communication is to report the occurrence of spontaneous, repeated histamine shocks, on two occasions causing unconsciousness, in an infant with urticaria pigmentosa. Since this complication of urticaria pigmentosa has not been previously described the clinical features as well as the results of the studies of the histamine metabolism will be reported. Following the surgical removal of two tumors suggestive of urticaria pigmentosa changes the histamine shocks disappeared. Since dog mastocytomas have been found to disappear upon cortisone treatment (F. Bloom) a trial with such therapy was made in our patient. The changes which were produced after local application of hydrocortisone will be described.

[1] This investigation was aided by a grant from the Gustaf and Tyra Svensson Memorial Fund.

[2] The authors wish to thank Mrs. M. Hasselgren for valuable technical assistance.

Fig. 1. The patient at the age of 10 months. Note the big, elevated and ulcerated lesion situated below the left clavicula. This is one of the tumorlike lesions which later on was surgically removed.

Case Report

Girl, M. W., 55.12.10. The parents and one older sister are healthy. At birth, the girl was found to have 4 red maculae, about one cm in diameter, localized to the trunk. The skin manifestations increased in number and size, and the colour changed from blue-red to brown. Itching did not seem to have been marked during the first few months of life. The lesions were typical of urticaria pigmentosa.

At the age of three months the patient had an attack of unconsciousness and was referred to the hospital because of suspicion of cerebral damage. The sequence of events was spontaneously described by the mother in the following way: There was a sudden general blush and the girl became extremely irritated. After a short while she became pale, flaccid and unconscious. There were no convulsions. The unconsciousness lasted for some minutes. At about the same time white papules with a reddened margin appeared over the original pigmentosa lesions. Some of the wheals were transformed into blisters, which during the course of a few hours became thinwalled and ruptured.

This sequence of events has later been observed several times, but only on two occasions the girl lost consciousness.

The patient was observed in this Clinic three times, at the ages of 5, 10 and 18 months, respectively.

Her physical and mental development was found to be normal. She had no lymphadenopathy, nor any enlargement of liver or spleen. Neurological investigation and ophthalmoscopy revealed normal findings. The urticaria pigmentosa lesions were distributed over the scalp, face and trunk (Fig. 1). Some of the lesions were infiltrated, showing a firm consistency, and a granulomatous surface. Others formed blisters which ruptured easily. There was no anemia, nor any eosinophilia or basophilia. No abnormalities were found in the cerebrospinal fluid. The electroencephalographic record was normal for the age. Roentgenological examination of the whole skeleton showed no signs of sclerosis nor the presence of any destructions.

Course and treatment.—At the age of 10 months two real tumors the size of almost half a hen's egg developed. At the same time the itching was almost unbearable. Between the ages of 10 and 12 months she repeatedly had acute severe attacks of restlessness. However, no general flush was noted.

In order to mitigate the itching and the other symptoms ascribed to histamine liberation, antihistaminics were given with some beneficial effect.

When the girl was 11 months old one of the tumor-like formations was removed but the itching and the attacks of restlessness remained.

Since ACTH has been demonstrated to cause a marked reduction in the number of tissue mast cells in man (Asboe-Hansen, 1950b) and since cortisone has been found to cause a prompt and complete disappearance of mastocytomas in dogs (F. Bloom), a trial with adrenocortical steroids was considered to be indicated, particularly because of the alarming symptoms of histamine shocks. Because of the risk of massive histamine liberation during the course of such therapy only local treatment was given. For 9 consecutive days hydrocortisone (Merck & Co, Inc.), in a dose of 12.5 mg, once a day was injected locally into the remaining tumor-like lesion. However, since there was no macroscopic effect upon the tumor and since the symptoms of the patient were almost as marked as before this treatment, this tumor-like formation was surgically removed.

A few days after the removal of this last tumor there was a remarkable change in the reactions of the patient. The intractable itching, as well as the attacks of restlessness, disappeared. The patient became quiet, slept well and there was no longer any need of antihistaminics. On control investigation, 6 months after the removal of this mastocytoma-like skin tumor, no signs of recurrence in loco were found.

Special Investigations

Heparine-like activity in the skin.—The fluid of the blisters was examined with reference to anticoagulant properties. However, with the technique described by Bassiouni no inhibition of clotting time was observed. No tissue material was investigated.

Histamine studies.—Free histamine was estimated in the urine as described by Dunér & Pernow. Histamine was adsorbed on a cation exchanger (Amberlite IRC-50) and eluated with hydrochloric acid. Isolated guinea pig ileum was then used for the quantitative estimation.

In two small urticaria pigmentosa lesions removed when the patient was 18 months old the histamine content was 50 and 60 μg per g tissue, respectively.[1] Thus, there was approximately a 10-fold increase when compared to normal skin (cf. Perry).

At an age of 18 months also the urinary excretion of histamine was determined in two different 12 hours periods. As is seen in Table 1 the urinary output of histamine was even on that occasion, when the symptoms of histamine release to the circulation had disappeared, much higher than in normal children. Unfortunately, no reliable histamine estimations were performed before the two tumor-like formations had been removed.

Studies on 5-hydroxytryptamine.—Since in some animal species the mast cells have been found to contain great quantities of 5-hydroxytryptamine (Benditt) the presence of this compound within the urticaria pigmentosa lesions was investigated. The urinary excretion of the 5-hydroxytryptamine metabolite 5-hydroxyindoleacetic acid was also estimated. These investigations were considered to be of special interest with reference to the pathogenesis of the pigmentations in urticaria pigmentosa since Blaschko & Hellman have shown that oxidation products of 5-hydroxytryptamine give rise to brown pigmentations.

The estimation of the urinary excretion of 5-hydroxyindoleacetic acid was performed as described by Macfarlane, Dalgliesh, Dutton, Lennox, Nyhus & Smith, using 1-nitroso-2-naphtol and nitrous acid as reagents. The 5-hydroxytryptamine assay was made on the same extract as that which was used for the estimation of histamine.

The extract from one biopsy specimen removed at an age of 18 months produced a contraction of guinea-pig ileum even after blocking of the histamine action with Lergitin. Since, however, this effect was not inhibited by the addition of dihydroergotamine, 5-hydroxytryptamine could not be the active principle (Gaddum & Hameed). Because of the limited amount of material available no further studies could be made.

As is seen from Table 1 the urinary output of 5-hydroxyindoleacetic acid was within the normal range.

Histologic examination of the tumor-like formations, with particular reference to the effect of hydrocortisone.—The biopsies were performed in narcosis in order to prevent the morphological changes which might be induced by local anesthetics. The specimens were fixed in various fluids such as 10 per cent neutral formalin, methanol and 4 per cent basic lead acetate combined with formalin or absolute ethanol and were then embedded in paraffin. The sections were stained with hematoxylin and eosin, toluidin blue, Giemsa and Klüwer–Barrera stains.

[1] The histamine was extracted from the tissue in acid ethanol according to Euler & Purkhold.

TABLE 1

Urinary excretion of free histamine and of 5-hydroxyindoleacetic acid in the patient with urticaria pigmentosa and in normal children of about the same age.

In the patient with urticaria pigmentosa the urinary excretion of histamine was estimated in samples collected during the night. Since histamine excretion in the urine is about twice as high during the day than at night (Dunér & Pernow) the difference between our patient and normals might be still more pronounced than can be judged from the values given. The values for the urinary output of histamine in normal children agree with those obtained by Adam & Mitchell.

	Histamine excretion μg per kg body weight	5-hydroxyindoleacetic acid excretion mg
Patient[a]	0.4 and 0.8 per 12 hours	0.5 per 12 hours
Normal children	0.21–0.40 per 24 hours[b]	0.2–3.0 per 24 hours[c]

[a] Estimated at an age of 18 months. For technical reasons it was only possible to obtain 12-hour samples.

[b] Four children investigated.

[c] Thirteen children investigated.

The biopsy specimen from the untreated tumor-like formation showed a characteristic skin infiltration, chiefly consisting of mast cells but also of eosinophils. As seen in Figs. 2 and 3 the gross appearance at low magnification varied considerably although the sections were from the same lesion. In some areas the mast cells formed dense masses within the connective tissue, often perivascularly and around hair follicles and sweat glands (Fig. 2). The number of eosinophils was moderate, chiefly located in lesions with accumulation of mast cells. In other areas (Fig. 3), however, a diffuse infiltration of mast cells within the corium and an enormous amount of eosinophils were found.

The epithelium of the epidermis showed a heavy pigmentation of the basal cells (Fig. 4).

The mast cells had the same appearance as in normal connective tissue. They were rather large with basophilic, metachromatic granules in their cytoplasm. Generally, their shape was oval but rounded or spindle-shaped forms were frequently found. Spindle-shaped forms were especially common among the bundles of connective tissue fibres in the corium. The nuclei of the mast cells were large and oval in shape. They stained well with basic dyes and one or several prominent nucleoli were usually seen. Binucleated mast cells were occasionally found.

Fig. 2. Photomicrograph (× 130) of an untreated urticarial lesion. Note the accumulation of mast cells in corium. Giemsa stain.

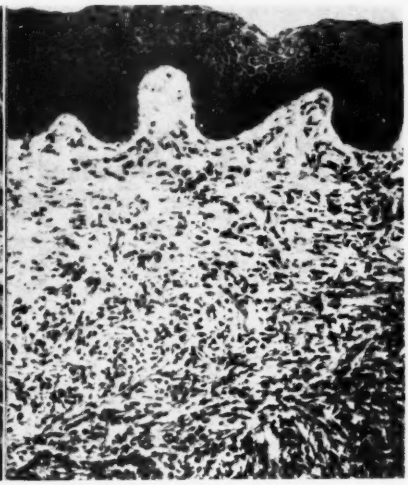

Fig. 3. Photomicrograph (× 130) of another section of the same lesion as that shown in Fig. 2. A diffuse infiltration of the corium by mast cells and some eosinophils is clearly seen. Giemsa stain.

Fig. 4. Photomicrograph (× 500) of the basal cells of the epidermal epithelium. Note the big content of pigments within these cells.

The eosinophils resembled in detail those seen in peripheral blood. They were smaller than the mast cells and contained a lobulated nucleus which stained intensely with basic dyes (Fig. 5). This facilitated their recognition even at lower magnifications. Their cytoplasm was filled with granules of about the same size as the mast cell granules but stained intensely with eosin.

Staining for the demonstration of iron pigments proved to be negative.

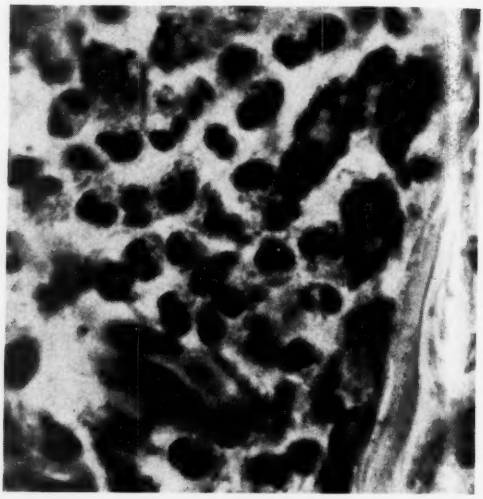

Fig. 5. Photomicrograph (× 1100) of a section from an untreated urticarial lesion showing typical mast cells with large oval nuclei and dark granules. A large number of eosinophils with smaller, frequently lobated, dark-staining nuclei and lighter granules are also seen. Giemsa stain.

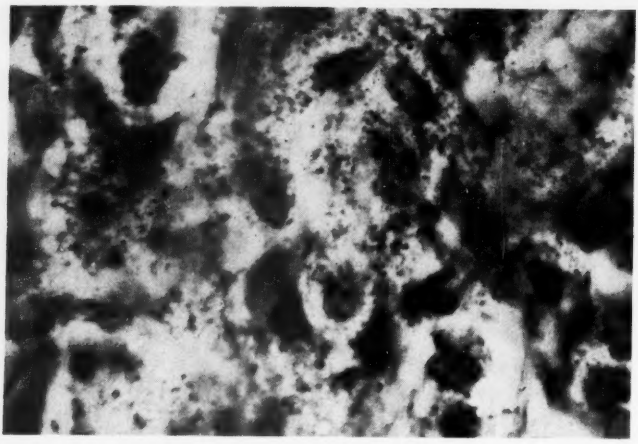

Fig. 6. Photomicrograph (× 1100) showing degenerative changes within the mast cells following local treatment with hydrocortisone. The cells have disintegrated and their granules are scattered in the intercellular spaces. Pycnotic cell nuclei are seen. Stained with Giemsa.

After local hydrocortisone treatment definite morphological changes were observed. The number of mast cells was not significantly reduced but marked cytological changes were observed. Within the mast cells degenerative changes characterized by disintegration and release of granules had developed (Fig. 6). The cell borders very often were not discernable and

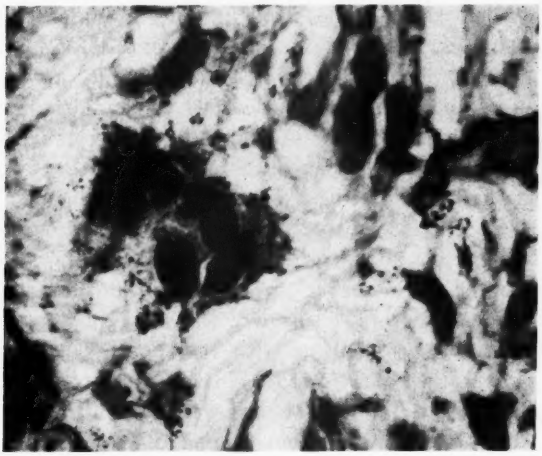

Fig. 7. Photomicrograph (×1250) of a multinucleated giant mast cell from an urticaria pigmentosa lesion treated locally with hydrocortisone. Giemsa stain.

vacuoles were common in the cytoplasmic remnants. Pycnotic nuclei within disintegrated mast cells were abundant. In some mast cells a definite decrease in the number of granules was noted but the cells still appeared intact. The interesting observation was made that following hydrocortisone treatment binucleated forms were common and trinucleated as well as multinucleated forms also occurred (Fig. 7). In such cells there were several granules which stained intensely with eosin among the few remaining intracellular ones.

After treatment with hydrocortisone the number of eosinophils was reduced to such an extent that they were rather scarce.

Discussion

The ease with which the triple response of Lewis is elicited on mechanical irritation of urticaria pigmentosa lesions demonstrates in an obvious way that the skin changes typical of this disorder contain great amounts of histamine and that this substance may very easily be released. In our patient the histamine content of the skin changes was also found to be very high, this finding being in accordance with the results which earlier have been obtained by West. The histamine most probably originates in the mast cells which are known to contain great amounts of this substance (Riley & West).

The finding that the urinary output of free histamine was abnormally high in our patient and also in all 7 other patients with urticaria pigmentosa

studied (Dunér, Hamrin, Pernow & Waldenström, unpubl., one patient preliminary reported by Waldenström, Pernow & Silwer) demonstrates that in urticaria pigmentosa there is not only a local histamine release upon mechanical irritation but also a constant flow of this substance into the circulating blood. Thus, on theoretical grounds, the possibility exists that histamine shocks may develop if the release of histamine into the blood is suddenly increased by one or another mechanism. Quite recently, Hamrin, in a preliminary report, has described the occurrence of shocks in a patient with urticaria pigmentosa following the ingestion of acetylsalicylic acid. From these observations he suggested that acetylsalicylic acid in those patients who are sensitive to this drug may cause a sudden massive liberation of free histamine with the subsequent development of shock. In our patient the characteristics of the attacks of unconsciousness were such that there is no doubt that they were caused by a sudden release of histamine. This statement is strengthened by the demonstration of a high urinary output of unconjugated histamine even after the removal of the two mastocytoma-like formations which may have been the princial histamine producers.

Since the mast cells contain both heparin (Jorpes, Holmgren & Wilander) and histamine (Riley & West) it is astonishing that there is no impairment of the hemostases in our patient with a massive histamine release, while in others with only minute symptoms of histamine liberation severe and even lethal bleedings have been reported (Gardner *et al.*). This fact might be explained by the findings of Bloom, Larsson & Åberg, that histamine *in vitro* blocks the anticoagulant effect of heparin in proportions larger than 20:1.

Histologically, the lesions in our patient were typical of urticaria pigmentosa, although the number of eosinophils was unduly high. These cells are regularly encountered at the local site of histamine release (cf. Riley) and may be concerned with the detoxification of histamine (Vaughn; Vercauteren & Blondé). Their abundance in our patient might be due to the existence of intense histamine liberation.

Local administration of hydrocortisone caused definite regressive changes within the mast cells, although the effect was not so striking as that earlier observed in dog mastocytomas. The difference might to some extent be explained by the fact that rather small doses of hydrocortisone were given to our patient. The definite effect upon the mast cells indicates, however, that a trial with cortisone, although in higher doses than given by us, might be indicated, particularly in cases with systemic involvement. As there might be risk of histamine liberation during the degradation of the mast cells, administration of antihistaminics seems to be advisable during the course of such treatment.

Summary

The presence of acute spontaneous histamine shocks in an infant with urticaria pigmentosa is reported. This complication in urticaria pigmentosa made its first appearance at three months of age. The histamine content of two skin lesions and the urinary excretion of histamine was markedly elevated. Local treatment with hydrocortisone in small doses gave rise to definite regressive changes within the mast cells. The symptoms of histamine release remained, however. Following surgical removal of two big mastocytoma-like formations all symptoms of spontaneous free histamine liberation subsided although numerous ordinary urticaria pigmentosa lesions still remained.

Chocs spontanés d'histamine dans des cas d'urticaire pigmentée.

On rapporte la présence de chocs aigus spontanés d'histamine chez un nourrisson ayant une urticaire pigmentée. Cette complication de l'urticaire pigmentée s'est manifestée pour la première fois à l'âge de trois mois. Le taux d'histamine de deux lésions cutanées, ainsi que l'excrétion urinaire d'histamine sont remarquablement élevés. Un traitement local à l'hydrocortisone, en l'administrant à de faibles doses, a donné lieu à des changements régressifs définis dans les mastzellen. Cependant, les symptômes d'un déchargement d'histamine subsistent. A la suite d'une ablation chirurgicale de deux grandes formations, ressemblant à une tumeur cellulaire du sein, tous les symptômes d'une libération d'histamine libre spontanée se sont affaiblis, bien qu'il y ait encore de nombreuses lésions ordinaires d'urticaire pigmentée qui subsistent.

Spontane Histaminschocke bei Urticaria pigmentosa.

Es wird über das Auftreten akuter spontaner Histaminschocke bei einem Kleinkind mit Urticaria pigmentosa berichtet. Diese Komplikation der Urticaria pigmentosa erschien zum erstenmal im Alter von 3 Monaten. Der Gehalt an Histamin in zwei Hauteruptionen und die Histaminausscheidung im Harn waren dentlich erhöht. Lokalbehandlung mit kleinen Gaben von Hydrokortison bewirkte ausgesprochene regressive Veränderungen in den Mastzellen. Die Symptome von Histaminauslösung blieben jedoch bestehen. Im Anschluss an die operative Entfernung zweier grossen mastozytomähnlichen Bildungen klangen alle Zeichen von spontaner Auslösung von freiem Histamin ab, obwohl zahlreiche gewöhnliche Urticaria pigmentosa Veränderungen weiterbestanden.

Histamina espontánea de la urticaria pigmentada.

Descripción de histaminias agudas espontáneas en un niño afecto de urticaria pigmentada. Dicha complicación apareció por vez primera a la edad de tres meses. El contenido histamínico de dos lesiones cutáneas y la excreción urinaria de histamina, acusaban un nivel notablemente elevado. El tratamiento local con hidrocortisona, en pequeñas dosis, provocó cambios definitivos de regresión intramastocelular. No obstante, persistieron los síntomas de liberación histamínica. Sucesivamente a la escisión quirúrgica de dos formaciones seudomastocitomatosas considerables, cesaron todos los síntomas e liberación espontánea de histamina, aunque persistieran numerosas lesiones ordinarias de urticaria pigmentada.

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Very Unequal "Identical" Twins

by GERT v. SYDOW and AIME RINNE

It is characteristic of monozygotic twins that they are principally identical in appearance as well as in manner of reactions and that this identity will be to a great extent maintained even under very different conditions of life. However, it has long been recognized that considerable differences can sometimes be already present at birth. The following case is an illustration of this.

Parents and a 9-year-old brother healthy. The mother, 35, during the last month of pregnancy presented a slight hypertension and albuminuria. Her expected date of delivery was July 31, 1956. On July 5th, after three hours labour, she was delivered of female twins at five minutes interval, both by crown presentation. *Twin A* weighed 1430 g; she was a slender, small infant in good general condition, somewhat lean with normal muscular tonus and colour; she cried and struggled vigorously. *Twin B* weighed 3380 g; she had a normal amount of fat, good muscular tonus and colour, moved actively and sucked energetically at the breast (Fig. 1).

The *placenta* (Figs. 2 and 3) was a grossly unequal monochorial diamniotic twin placenta measuring 24 × 24.5 × 0.7–2.0 cm. The larger part had a thick oedematous umbilical cord, the smaller part a thin wrinkled cord. Approximately one-fifth of the smaller part showed an old marginal infarction measuring 13 × 6 cm. There were three umbilical vessels in each cord. Adjacent to the larger cord there was a subchorial deposit of fibrin covering an area 2 × 4 cm. A small surface arterial anastomosis was present between the two fetal circulations.[1]

Twin A was transferred immediately after birth to the Children's Hospital. For the first 5 days she was fed by gavage, then by teat, and from 2 weeks of age at the breast. Her lowest weight was 1370 g when 3 days old. Between 3 and 14 days old she was more icteric and dull than her sister but still more alert and "mature" than is usual for such a low weight. Her blood values were also all the time lower than those of her sister (Table 1). On discharge at 5 weeks of age she weighed 2220 g and suckled all her need from her mother. *Twin B*, who was all the time fed at the breast, had her lowest weight, 2980 g, on her fifth day of life and, on discharge, weighed 4000 g.

At home both the sisters were nursed entirely at the breast for about 3 months and were thereafter mixed-fed until 5 months of age, the smaller Twin A until 6 months

[1] For the examination of the placenta we are indebted to *Biörn Ivemark*, M.D., Pathological Dept., Karolinska Sjukhuset, Stockholm.

Fig. 1.

of age. Twin A was also given an iron preparation which, however, caused diarrhoea and, therefore, was not taken regularly. From 5 months of age Twin A has gradually developed a moderate seborrhoic dermatitis of the scalp, face, abdomen, and thighs; Twin B shows only a very slight dermatitis of the scalp. Twin A has all the time been more irritable and unquiet than her sister, sleeping less and less contentedly. Their development and their manner of playing etc., has run closely parallel, Twin B, however, always being some two weeks before Twin A. At 10 months Twin B was able to stand with support, but not Twin A. As appears from Table 1, Twin A has remained smaller and more anaemic than Twin B throughout the observation period. Roentgenograms of the wrist at 4 and 10 months showed no signs of rickets in either twin but the development of the ossification centres at 4 months was more advanced in Twin B.

A *serological examination* (performed at the Rh Laboratory, State Chemico-Forensic Institute) gave the following results:

"Father: A_1 MN P(+) Rh(+) type Rh_1Rh_2;
Mother: A_1 N P(+) Rh(+) type Rh_1rh;
Both twins: A_1 MN P(+) weak Rh(+) type Rh_1rh.

A calculation made at the Blood-group Genetical Section of the Institute demonstrated an approximately 88 per cent possibility for the twins being monozygotic."

Discussion

The examination of the placenta leaves no doubt that this pair of twins is monozygotic and this conclusion is also supported by the blood group

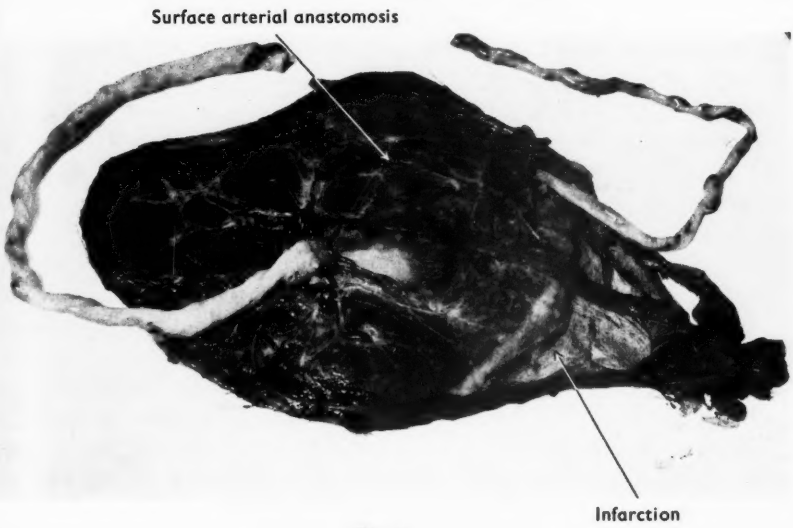

Fig. 2.

Fig. 3.

determinations. The examination of the placenta has further established that it belongs to the commonest type of monozygotic twins, the monochorial-diamniotic type.

Probably depending on at what time twinning was initiated, a mono-

TABLE 1

Age ...	Twin A 0 d.	1 d.	1 w.	2 w.	3 w.	4 w.	5 w.	4 m.	5 m.	10 m.	Twin B 0 d.	1 w.	2 w.	3 w.	4 w.	5 w.	4 m.	5 m.	10 m.
Weight	1430		1420	1570	1720	1910	2210	5610	6200	8350	3380	3150	3170	3450	3650	3880	7690	8070	10,710
Height	43							64½	65	73	50						69	70	77
Hb g %	18.8	19.1	21.3	18.2	13.4	9.8	9.2	7.7	8.7	8.4	23.9		20.2	14.8	14.2	13.4	12.4	11.4	10.7
Erythrocytes		4.0			3.9	2.9	2.7	2.6	3.5	3.2	5.5			4.3		4.1	3.7	3.7	3.6
Haematocrite					48			28		30				53			45		34
Leucocytes	18,100			9500	7000		6800	8500	19,000	9400	22,300		8700	9700		6700	10,600	8900	12,800
Icterus index			1: 64		1: 30							1: 40		1: 12					
Non-protein nitrogen					27			27						24			24		
Electrophoresis:																			
Serum																			
Total protein						4.5									5.1				
Albumin						2.94									3.19				
α_1-globulin						0.28									0.30				
α_2-globulin						0.36									0.43				
β-globulin						0.38									0.50				
γ-globulin						0.53									0.68				
Serum calcium						9.7			10.1						10.3				9.2
Serum inorg. phosphorus						7.0			7.8						6.8				7.6
Serum alk. phosphatase activ.						24.5			13.0						20.2				14.4

zygotic pair of twins will be (*a*) dichorial, (*b*) monochorial-diamniotic, or (*c*) monochorial-monoamniotic (5). Dichorial twins—where the twinning is supposed to have occurred during the morula stage or still earlier—are not to be differentiated from dizygotic twins at birth by aid of the secundines, but it should be possible at a later stage to differentiate them by serological tests and certain similarity methods. The dichorial twins have been estimated to include about 33 per cent of all live-born monozygotic twins (3). The monochorial-monoamniotic twins have developed late, after the formation of the amniotic sac. They also include all the conjoined twins. They have a high prenatal mortality rate because of intertwining of the cords and subsequent obstruction of circulation.

Price (6) discerns three chief kinds of "primary bias" known or presumed to affect the early development of twins: natal factors, lateral inversions, and effects of mutual circulation. *Natal factors* may hit all types of twins. *Lateral inversions* (genotypical asymmetries of Dahlberg (2)) may probably occur in all types of monozygotic twins but, theoretically, they ought to be expected more often the later scission has occurred; and they are known to be especially frequent in conjoined twins. The *effects of mutual circulation* seem to be of special interest in the present case.

In his basic work on this subject Schatz (7), in all monochorial placentas he examined, observed *capillary connections* (Zottentransfusionsströme) between arteries in one placental half and veins in the other. Further, he observed in a great number of cases *macroscopical anastomoses* between arteries of the two placental halves and in a few cases similar anastomoses between veins. Through these capillary connections a certain portion of the blood from the heart of one twin must flow into the circulatory system of the other. The large anastomoses have been supposed to have an equalizing influence on this imbalancing mechanism; at least this applies to the arterial anastomoses where blood is always running in the direction from the more vigorous twin to the weaker, until the latter is no longer the weaker; this has been supposed to explain why monochoriotic twins, as a rule, are fairly equal (9).

Sometimes, however, this equalizing mechanism may be supposed to fail to appear or to be insufficient. It seems natural to think that in such cases the result must be an unequal supply of oxygen and nutrition during fetal life as well as an unequal amount of blood and iron stores at birth in the two twins. It is known that a qualitatively excellent but quantitatively insufficient nutrition may result in dwarfing but otherwise normal development; an illustrative experiment was recently demonstrated (10) where two littermate pigs had been reared on exactly the same first class diet, but one in very restricted amounts: at 12 months of age this pig weighed 12 kg, the

brother 260 kg; both were said to be equally alert, the only difference being that the small pig had a steady subnormal temperature. A similar effect may well be supposed to result from a steady withdrawing of blood from one twin to the other *in utero*.

In our case the smaller twin, besides being retarded in growth, also presented a slight anaemia. Similar cases have been reported by Herlitz (4) and by Bergstedt (1) where one monochorial twin was considerably smaller at birth than the other and anaemic. Herlitz interprets the anaemia as a result of the mutual circulation during fetal life and this assumption is supported by the fact that in one of his cases the placental half of the anaemic twin was also remarkably pale. Bergstedt, on the other hand, seems to mean that the transfer of blood from his smaller Twin II *via* the placenta to the larger Twin I has mainly taken place after the birth of the first twin. This explanation cannot be applied to the anaemia in the first twin in our case and in one of Herlitz's cases. On the other hand, Seip (8) postulates that usually the last-born twin has a higher haemoglobin and erythrocyte count of the peripheral blood than Twin no. 1, which is assumed to be due to an extra "blood transfusion" to the last-born twin from the placenta, caused by the more complete contraction of the uterus when the last fetus is delivered. This is hardly in accordance with our experience, nor with the findings in two of the above-mentioned cases.

In all these four cases it was the smaller twin who was anaemic. During the last year we have observed two further pairs of monochorial-diamniotic twins with the same combination in both, which might suggest that this is the rule. In the first pair, the birth weights were 1870 and 2870 g and the haemoglobin values at 2 weeks of age 18.2 and 24.4 g per cent, respectively; in the second pair, the birth weights were 2900 and 2280 g and the Hb values 28.8 and 18.9 g per cent, respectively. At 9½ months of age in the first pair the weights were 7780 and 8150 g and the Hb values 9.9 and 13.9 g per cent, respectively.

The combination in six pairs of monozygotic twins of retarded growth and anaemia in one twin may suggest that the anaemia and the retardation of growth have a common cause. Can it be supposed that the mutual circulation observed in the six placentas can also have resulted in different blood values in the two twins at birth? Admittedly, *in utero* the circulatory systems of the twins are to be regarded as communicating vessels and, accordingly, must contain fluids of identical composition. At birth, then, the blood values must be identical in both, provided that nothing interferes with this balance during delivery. Anaemia in one twin at birth, accordingly, must depend on some mechanism of the sort proposed by Bergstedt (1) or by Seip (8). On the other hand, in none of the six cases referred to above

have blood values been obtained from the cord; it is possible, therefore, that the difference between the twins observed somewhat later might have arisen after birth. This could be explained by the supposition that, though the composition of the circulating blood at birth be identical in the two twins, the amount of blood and the storage of iron was different; and such a difference might well be the result of the same mechanism as caused the difference in growth during fetal life. In the three cases observed by us the "anaemia" in the smaller twin was not very marked during the newborn period; it would perhaps be more correct to speak of a "polycythaemia" in the bigger twin. But the anaemia has afterwards aggravated and in the two cases observed for ten months has persisted through this time. This, in our opinion, speaks in favour of the hypothesis that the anaemia in the smaller twin is caused by a deficient storage of iron during fetal life, probably as a result of the imbalanced mutual circulation between the placental halves.

It has to be admitted, however, that this is not the only possible explanation of the difference in growth and blood values between monochorial twins. The difference may possibly also be explained by different placentation or by genotypical asymmetries. Whatever the explanation, it is interesting to note that in originally "identical" twins some environmental factor acting during fetal life may result in a difference in growth and blood values which may persist for a long time after birth.

Summary

A pair of monochorial-diamniotic twins of very unequal size and blood values at birth is reported. The birth weights were 1430 and 3380 g and the haemoglobin values on the first day of life 18.8 and 23.9 g per cent, respectively. These differences between the twins have persisted during ten months of observation; at ten months, the weights were 9400 and 10,710 g and the Hb values 8.4 and 10.7 g per cent, respectively. Similar findings in monochorial twins have been collected from three cases reported in the literature and from two further cases seen by the authors. It is believed that the differences may be due to some environmental factor acting during fetal life, most likely the effects of the mutual circulation between the placental halves, by which one twin was starved *in utero* and was born with an insufficient storage of iron.

Jumeaux monozygotes très différents.

L'auteur donne la description du cas de deux jumeaux monozygotes dont la taille et la formule sanguine étaient très différentes à la naissance. Leurs poids à la naissance étaient respectivement de 1430 et 3380 grammes tandis que leurs taux d'hémoglobine au premier jour s'élevaient respectivement à 18,8 et 23,9 g %. Ces différences subsistèrent tout au long des dix mois durant lesquels ces jumeaux furent gardés en observation. A l'âge de 10 mois, ils pesaient respectivement 9400 et 10 710 grammes et leurs taux d'hémoglobine s'élevaient respectivement à 8,4 et 10,7 g %. Des observa-

tions similaires concernant des jumeaux monozygotes ont été relevées dans trois cas décrits dans la littérature ainsi que dans deux autres cas observés par les auteurs. On suppose que ces différences pourraient être dues à l'intervention d'un facteur du milieu au cours de la vie fœtale et plus que probablement à un effet de circulation réciproque entre les deux portions placentaires à la suite duquel un des jumeaux a été insuffisamment alimenté et est venu au monde avec des réserves de fer insuffisantes.

Sehr ungleiche „identische" Zwillinge.

Es werden zwei monochoriale diamniotische Zwillinge beschrieben, die bei der Geburt verschiedene Grösse und Blutwerte aufwiesen. Das Geburtsgewicht betrug 1430 bzw. 3380 g und die Hämoglobinwerte am ersten Lebenstag 18,8 und 23,9 g per Hundert. Diese Unterschiede zwischen den Zwillingen bestanden während der 10monatigen Beobachtungszeit weiter. Im Alter von 10 Monaten war das Körpergewicht 9400 bzw. 10710 g und die diesbezüglichen Hämoglobinwerte betrugen 8,4 und 10,7 g %. Ähnliche Befunde bei monochorialen Zwillingen wurden von drei im Schrifttum veröffentlichten Fällen und zwei weiteren von den Autoren beobachteten Fällen zusammengebracht. Es wird angenommen, dass die Unterschiede auf Faktoren in der Umgebung, die während des fötalen Lebens einwirken, zurückzuführen sein könnten, am wahrscheinlichsten Störungen im gemeinsamen Kreislauf zwischen den beiden Plazentahälften, wodurch ein Zwilling in utero ausgehungert wird und mit einem unzulänglichen Eisenvorrat zur Welt kommt.

Gemelos "idénticos" muy desiguales.

Dos gemelos diamnóticos monocoriales de muy desiguales tamaños y valores sanguíneos al nacimiento. Peso al nacer: 1430 y 3380 g; valores de hemoglobina el primer día de la vida, 18,8 y 23,9 g por ciento, respectivamente. Estas diferencias persisten entre los gemelos durante diez meses de observaciones. A los diez meses, pesos de 9400 y 10710 g; valores de hemoglobina, 8,4 y 10,7 g por ciento, respectivamente. Se han registrado datos análogos acerca de gemelos monocoriales en tres casos descritos en la literatura y en dos otros casos observados por los autores. Se cree que las divergencias pudieran atribuirse a algun factor ambiente durante la vida fetal, siendo lo más probable que se deban a los efectos de la circulación recíproca entre las mitades placentarias, por lo cual un gemelo ha sufrido a expensas del otro en la matriz y ha nacido con insuficientes reservas de hierro.

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Aimed Antibiotic Treatment of Pneumonia on the Basis of Tests Carried out with Subglottic Swabs

by B. STEINER, G. PUTNOKY, KLÁRA KOVÁCS, J. SZABON

The successful treatment of pneumonia is dependent on several factors. One of the most significant of them is the adequate selection of the antibiotic the causative agent is most sensitive to. With pneumonia cases in children we generally test the nasopharyngeal cultures, a procedure which lends ample support for a differentiation of the causative agent. Thus, in most cases, mixed cultures are produced rather than pure growths.

Since, in all probability, proceeding towards the lung the number of saprophytes in the airways decreases, it is better to search for causative agents in the bacterial culture of the lower air passages. It is obvious that, proceeding in this way, we should find predominant or pure cultures rather than mixed ones normally present in the throat swabs, causative agents instead of saprophytes. We hoped that, taking subglottic tests into consideration, we might come nearer to the fulfilment of our set task, the aimed antibiotic treatment of pneumonia.

Method

The swabs to be tested have been taken from the nose, from the pharynx and from the larynx by means of a sterile diphtheria stick and from the subglottic tract with a Haslinger laryngoscope by means of suction. The organisms have been cultured on human blood and chocolate agar. The sensitiveness to penicillin, streptomycin, threomycin and terramycin of the bacterial culture has been differentiated by means of diffusion.

In the case of test material yielding mixed cultures, their tribes have not been differentiated in our present work and thus the sensitiveness to antibiotics of the isolated pure cultures has not been defined. As a matter of course we have been well aware that, from a scientific point of view, the sensitiveness to antibiotics of the individual strains of organisms ought to have been specified. However, we aimed simply at examining whether, for everyday life, defining the sensitiveness of the organisms not only of a pure culture but also of a mixed one would be adequate.

Results

Within the period from 1st October 1954 to 1st August 1955, the subglottic swabs taken by suction from altogether 87 children with pneumonia have been tested in our ward. For the sake of comparison, in 66 cases we have taken also throat and larynx swabs.

According to their age, the patients have been grouped as follows:

16 infants from 0 to 1 year of age
22 children from 1 to 2 years of age
29 children from 3 to 6 years of age
20 children from 6 to 14 years of age.

After having established the diagnosis and taken the bacteriological test material, antibiotic treatment was started immediately.

The result was that the treatment was successful even with an antibiotic to which the organism was not sensitive *in vitro*. As a matter of course, in such cases we did not change the antibiotics. If, however, the treatment that was started proved unsuccessful, we changed the antibiotics in each case, according to our original program, taking into consideration the subglottic findings.

In order to demonstrate whether our recovery rates rise in consequence of sucking subglottic swabs, we wish to group our data as follows. To begin with, we compared the resistance test of throat, larynx or subglottic swabs. The data agreed entirely or partly, but in some cases they were entirely different.

According to our records, there is no marked contrast between the sensitiveness to antibiotics of the bacterial cultures taken from the different places. For instance, comparing the sensitiveness to antibiotics of the organisms cultured from larynx and throat swabs in 66 cases, in 29 cases full conformity was observed, in 27 cases partial conformity, and in 7 cases entire dissimilarity, whereas in 3 cases the throat swabs proved sterile. Comparing throat and subglottic tests in 66 instances, we observed full conformity in 29 cases, partial conformity in 26 cases, no conformity at all in 9 cases, and the agars inoculated with subglottic swabs remained sterile in 2 cases. Thus we observed dissimilarity between the test of the throat and the subglottic swab in nine out of 66 cases.

Comparing the results of the applied treatment and those of the resistance tests, we made the following observations: in 59 out of 87 cases the treatment, started without knowing the bacterial culture, proved successful. It is, however, both curious and remarkable that the antibiotics used successfully in treatment conformed only in 36 cases with those which proved successful in resistance tests, in 23 patients the antibiotic applied proved successful

even when, according to *in vitro* tests of the subglottic culture, another antibiotic ought to have been given.

Summing up our data, it can be stated that antibiotic treatment started before receiving the resistance test proved unsuccessful in 28 cases. In these cases a change of the antibiotics was effected on 24 occasions on the grounds of tests carried out to define the resistance to antibiotics of the subglottic bacterial culture, and on 4 occasions (when the subglottic culture remained sterile) on the grounds of resistance tests of the glottic flora. It could be stated that *the treatment effected in this manner proved successful in all cases.* This is remarkable when it is considered how frequently good results were observed even in cases when the treatment was carried out succesfully with antibiotics which, in *in vitro* tests, proved inadequate.

Discussion

In order to carry out the treatment aimed at, first of all the causative agent must be isolated, and after that comes the selection of the suitable antibiotics. According to Binder *et al.*, in 42 out of 67 cases pure or predominant cultures were yielded whereas on 25 occasions non-characteristic mixed cultures grown from the larynx swab were yielded. Since we cannot carry out regular demonstration and identification of viruses, an error as to the isolation of the causative agent of pneumonia may easily occur. In other cases, in spite of a pure culture of Klebsiella pneumoniae, our clinical diagnosis pointed to interstitial pneumonia and aspiration pneumonia, respectively. The first diagnosis was confirmed by necropsy, the second by removal of the foreign body (Steiner & Putnoky, 1956.)

As mentioned above, we could not isolate in all cases the supposed causative agent in pure culture from the throat and larynx swabs. We hoped to find the real causative agent rather in the lower air passages. According to our record now under publication (Putnoky *et al.*) the subglottic swab can be used for this purpose rather than the throat and larynx swab.

First of all, the question must be raised, how many times the treatment was successful without the co-operation of the laboratory. The result is that 59 out of 87 cases were cured. However, taking into consideration the fact that only serious cases, or those with which the home treatment was not successful, were sent to hospital, this result cannot be regarded as characteristic of general practice. Thus, the cases observed were all more serious than the average. It was remarkable that on 23 occasions the treatment started by us was successful, although—according to tests carried out *in vitro*—the antibiotic or antibiotics were not adequately selected. This raised a curious problem. We regarded it as a drawback that, in the

beginning, the resistance tests were obtained relatively late. This was a disadvantage in as much as the antibiotic to be applied could not be selected on grounds of the *in vitro* tests, yet, on the other hand, it was advantageous because the treatment which proved to be clinically right, was not changed unnecessarily.

Our data prove that—at least with our methodology—the claim, according to which treatment of pneumonia in infants and children is to be directed in all cases by the *in vitro* test, cannot be accepted. More than once we observed that although the causative *staphylococcus* had been declared as penicillin resistant by laboratory tests, by the time the test reached us penicillin treatment was already being applied with success. In such cases either a wrong causative agent was isolated, and thus the sensitiveness to antibiotics of the wrong causative agent was indicated, or, working with a mixed culture, the behaviour of the right agent became indistinct, or, though the antibiotic seemed to be ineffective, in consequence of primitive. *in vitro* conditions, it proved successful due to the strength of the organism.

In 15 out of 87 cases modification of the therapy was necessary. In six instances combined treatment started by us proved to be wrong; instead of combined treatment a third antibiotic had to be applied. In two cases only one of the antibiotics applied in combined treatment was necessary, and only in one single case did we add a third one to the two antibiotics. In four cases the subglottic swab was negative, i.e. proved to be sterile; here the *in vitro* test could give no help in the question of a change. In spite of the relatively small number of cases, our records point to multiple and radical changes. Without *in vitro* tests we should have gone further with our experiments unless bacteriological blood tests had failed to support us.

If the results of the throat swabs had been considered competent, the treatment, in all probability, would have been less frequently successful than the therapy applied on the basis of the subglottic tests. This is due to the fact that the bacterial flora of the subglottic mucosa is not so rich. In this place apathogenic organisms live in a smaller number. From this mucosa we can isolate pathogenic bacteria more often than from the throat mucosa. The correctness of this opinion is verified by data taken from our ample material (Putnoky *et al.*).

We could isolate *diplococcus pneumoniae*, members of the *streptococcus viridans* and Neisseria group, and monilia less frequently from the mucosa of the subglottis than of the throat. The blood and haemoglobin agar plates inoculated with secretum of the subglottic mucosa proved sterile three times as often as the plates inoculated with throat material. These data shows the relative poverty of the subglottic bacterium flora. Comparing in 93 cases the throat culture with the subglottic flora on the basis of their

supposed pathogenic power, 20% yielded equivalent cultures whereas in 50% of the cases the subglottic culture had a greater value. Comparing the glottic with the subglottic culture in 180 cases, 41% yielded equivalent cultures, but in 33% of the cases the subglottic flora proved to be of greater value than the glottic one. These data prove that the subglottic flora, as regards its supposed pathogenic power, is more valuable than the throat and the glottic flora. Thus, we can isolate pathogenic organisms more frequently and with greater safety from the subglottic than from the throat or glottic mucosa.

In connection with this observation, it is remarkable that, while our treatment proved successful on 23 occasions even though—according to *in vitro* tests—an inadequate antibiotic was applied, in uncured cases the change of antibiotics effected on the basis of *in vitro* tests of the subglottic culture proved successful in each individual case. In order to find an explanation to this fact, it must be emphasised again that the source of error in *in vitro* tests is relatively frequent. In our attempts this source of error was eliminated by not changing the antibiotic if the treatment was successful. On the other hand, when the treatment was unsuccessful not only the *in vitro* test but also the *in vivo* observations pointed to the application of an inadequate antibiotic or to the inadequacy of the combination of antibiotics. Thus, the selection of antibiotics was then made on the basis of a double system of tests, i.e. biological and laboratory tests.

According to our subsequent records, efficient change of treatment was more often indicated by tests of subglottic swabs than on the basis of findings of the throat swabs. Thus, it is obvious that tests of the subglottic swabs are more reliable than those made with throat cultures.

Summary

Eighty-seven infants with pneumonia were treated and all recovered. The causative agent has been ascertained by tests carried out with the throat, the glottic and the subglottic bacterial culture.

The subsequent comparison of the tests of the throat and subglottic swabs makes clear that aimed treatment amended on the basis of knowing the bacterial culture grown from the subglottics swabs and the resistance to antibiotics of this culture is more efficient than that which would have been effected on the basis of tests made on throat swabs.

Traitement poursuivi d'une pneumonie avec des antibiotiques, en se basant sur des tests mis en exécution avec des prélèvements subglottiques.

On rapporte 87 cas de pneumonie chez des nourrissons. L'agent causatif a été constaté par des tests mis en exécution à l'aide de cultures bactérielles glottiques, subglottiques et de celles provenant de la gorge. Au troisième jour de l'affection, on a pu

dire si la thérapeutique appliquée peut être considérée comme une réussite ou non. Il a été affirmé que dans 59 sur 87 cas, le traitement, commencé sans connaître la culture bactérielle et les tests de résistance, semble être un succès. Il est remarquable que les antibiotiques, appliqués avec succès du point de vue clinique, correspondent seulement dans 36 cas à ceux dont l'efficacité a été prouvée par des tests de résistance. Dans 23 cas, ils sont différents. Dans 28 cas, la thérapeutique, en la commençant sans connaître la culture bactérielle et les tests de résistance, est sans succès. Dans 24 de ces cas ci, également les tests de résistance, exécutés in vitro avec la culture subglottique, indiquent l'insuffisance de sélection des antibiotiques. Dans 4 cas, les agars demeurent stériles. Selon toute probabilité, ceci est dû au fait que dans de tels cas, les antibiotiques ont été sélectionnés en se basant sur des tests doubles : des tests in vitro et in vivo. La comparaison, exécutée par la suite, des tests avec des prélèvements subglottiques et ceux provenant de la gorge, explique que le traitement poursuivi s'améliore en connaissant la culture bactérielle cultivée du prélèvement subglottique, et que la résistance aux antibiotiques de cette culture est plus efficace que celle qui aurait été effectuée en se basant sur des tests faits avec des prélèvements provenant de la gorge.

Zielsichere Behandlung der Pneumonie mit Antibiotika, auf Grundlage von Testen mit Abstrichen aus der Subglottis.

Bericht über 87 Kinder mit Pneumonie. Das ursächliche Agens wurde mit Hilfe von Testen, die mit Bakterienkulturen aus dem Rachen, der Glottis und Subglottis durchgeführt worden waren, festgestellt. Am dritten oder vierten Tag der Krankheit konnte entschieden werden, ob die angewendete Behandlung als erfolgreich oder erfolglos angesehen werden sollte. Bei 59 unter den 87 Fällen wurde die Behandlung ohne die vorherige Kenntnis der Bakterienkultur begonnen und die Resistenzproben erwiesen sich erfolgreich. Es war bemerkenswert dass die von klinischen Gesichtspunkt mit Erfolg angewendeten Antibiotika nur in 36 Fällen mit denen übereinstimmten, deren Wirksamkeit mit Hilfe von Resistenzproben nachgewiesen wurde. In 23 Fällen waren sie verschieden. Bei 28 Fällen, in denen die Behandlung ohne Kenntnis der Bakterienkultur und der Resistenzproben begonnen wurde, erwies sie sich als verfehlt. In 24 dieser Fälle wiesen auch die in vitro durchgeführten Resistenzproben mit Bakterien aus der Subglottis auf die unzulängliche Auswahl der Antibiotika hin. In 4 Fällen blieb die Agarplatte steril. Das ist wahrscheinlich auf die Tatsache zurückzuführen, dass die Auswahl des Antibiotikums auf Grund doppelter Teste — in vitro und in vivo — getroffen wurde. Der folgende vergleich zwischen Testen mit Abstrichen vom Rachen und von der Subglottis lässt es klar erscheinen, dass eine zielsichere Behandlung, korrigiert auf Grund der Kenntnis der Bakterienkultur aus der Subglottis und der Resistenz dieser Kultur auf Antibiotika wirksamer sei, als eine sich auf Testen mit Rachenabstrichen gründende Behandlungsmethode.

Perspectivas de tratamiento antibiótico de la neumonia por pruebas a base de tapones subglóticos.

Casuística de 87 niños afectos de neumonía. El agente causante ha sido determinado por pruebas llevadas a cabo con cultivo bacterial de garganta, glotis y subglotis. Desde el tercer a cuarto día de enfermedad, pudo pronosticarse el éxito o fracaso de la terapéutica practicada. Se menciona que en 59 de los 87 casos, el tratamiento se inició sin conocerse el cultivo bacterial ni las pruebas de resistencia y que resultó feliz. Merece

especial mención el hecho de que los antibióticos, aplicados con éxito desde un punto de vista clínico correspondieron en 36 de los casos solamente con aquellos cuya eficacia fué comprobada por pruebas de resistencia. En 23 de los casos fueron diferentes. En 28 otros, al iniciarse la terapéutica sin el conocimiento del cultivo bacterial ni de las pruebas de resistencia, la primera resultó inefectiva. En 24 de estos casos, las pruebas de resistencia in vitro del cultivo subglótico demostraron lo inadecuado de la selección de los antibióticos. En 4 casos el agar permaneció estéril. Muy probablemente se atribuye esto al hecho de que en tales casos, la selección del antibiótico se efectuó sobre base de pruebas dobles: pruebas in vitro e in vivo. El estudio comparativo subsiguiente de los tapones de garganta y subglotis, pone en evidencia que el tratamiento a perseguir, modificado de acuerdo con el conocimiento adquirido del cultivo bacterial desarrollado por el tapón subglótico y la resistencia de este cultivo a los antibióticos, es más eficaz que el que fuese efectuado fundándose en pruebas realizadas con tapones de la garganta.

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Importance of the Quantitative Determination of Direct and Indirect Bilirubin in Hemolytic Disease of the Newborn

by V. JIRSOVÁ, M. JIRSA and M. JANOVSKÝ

Until recently it has not been possible to evaluate the significance of serum determinations of direct and indirect bilirubin, since the mechanism of diazotisation of direct and indirect bilirubin was not known.

It has recently been shown that the direct diazo reaction of bilirubin depends upon changes in its physical state in solution (2, 3, 4). Indirect bilirubin does not react with the diazo reagent because in solution it exists in a combined colloidal form. A prerequisite for primary diazotisation of bilirubin is a monomolecularity, i.e. its complete solubility even in an acid medium, in which the diazo reaction occurs. Monomolecularity is obtained when bilirubin is in combination with a polar molecule, as has been demonstrated experimentally with the conjugation of bilirubin with taurin and glycocol (5, 6). Recent isolation studies have shown that the conjugating substance for bilirubin in the body is glucuronic acid (1, 8, 10). Both forms of bilirubin in serum are bound to albumin.

On the basis of these new findings, which have thrown light upon the nature of direct and indirect bilirubin, it would appear, that routine estimation of both forms of bilirubin in clinical practice might contribute to greater understanding of the metabolism of bile pigments.

In this communication we present data illustrating the course of direct and indirect bilirubin levels in 32 infants with a hemolytic disease of the newborn.

Methods

A modification of the method of the Malloy & Evelyn (7) was used for the quantitative determination of direct and indirect bilirubin.

The method used was as follows:

1. To 0.4 ml of serum in test tube "A" add 8.6 ml distilled water.
2. 1.5 ml of this diluted serum is pipeted into test tube "B".

3. To test tube "A" add 0.5 ml of diazo-blank (15 ml conc. HCl in 1000 ml distilled water).
4. To "B" add 0.5 ml of diazo reagent. (Solution I: 1.0 g of sulfanilic acid in 1000 ml distilled water containing 15 ml conc. HCl. Solution II: 0.5% sodium nitrate. The diazo reagent is freshly prepared by adding 0.3 ml sol. II to 10 ml of solution I.)
5. After 30 minutes transmission for direct bilirubin is read in a Leitz photocolorimeter at 550 mμ.
6. 5 ml of methyl alcohol is then added to both tubes "A" and "B".
7. After 30 minutes the transmission for total bilirubin is read using the same filter.
8. The per cent transmission is used to calculated bilirubin from a calibration curve prepared using bilirubin Hoffmann La Roche in chloroform-alcohol solution according to Malloy & Evelyn. The standard curve from 0.1 to 0.9 mg%.

Calculations:

Direct bilirubin in mg% = the value read from the calibration curve × 25.
Total bilirubin in mg% = the value read from the calibration curve × 50.
Indirect bilirubin = total—direct.

Results

Various types of curves of serum levels of total and direct bilirubin are illustrated in Figs. 1–5. The first few days after birth bilirubin levels were determined daily, and later at longer intervals.

The first two infants (Figs. 1 and 2) presented the picture of hemolytic disease of the newborn as usually seen in full term infants. These infants were in good clinical condition, had a typical history for erythroblastosis and had icterus, which appeared soon after birth. Bilirubinemia rapidly increased, but hemoglobin levels were not strikingly low. After exchange transfusion findings rapidly returned to normal.

In these two cases one can see that indirect bilirubin by far predominated. The levels of direct bilirubin were negligible.

Slightly higher levels of direct bilirubin were found in infant S. (Fig. 3) with a more severe form of erythroblastosis fetalis. The total bilirubin in cord blood was 7.25 mg%, of which 1 mg% was direct bilirubin. The infant was very anemic with a cord hemoglobin of 5.3 g (35%) and the liver enlarged 3 cm and spleen 2 cm below the costal margin. Total serum bilirubin reached its highest level, 21.1 mg%, on the second day after exchange transfusion and direct bilirubin reached 5.6 mg% on the fourth day. From the fourth day serum bilirubin fell to normal levels with rapid improvement in the general condition. The infant was discharged on the 11th day in good clinical condition.

In the last two infants a very severe form of hemolytic disease of the newborn was involved and these cases deserve more detailed analysis.

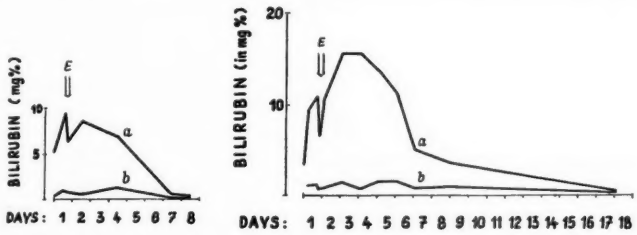


Fig. 1 and 2: a–total bilirubin, b–direct bilirubin, in the serum of full term newborn infants with usual course of hemolytic disease. E-exchange transfusion.

Infant Ka. (Fig. 4) was born at home, 17.3.1957, the fourth child. The mother's blood group was B Rh negative. Antibodies were not followed during pregnancy but were present in high titre after birth. Three siblings were healthy. The infant was born prematurely, birth weight 2400 g, length 45 cm. He was admitted 10 hours after birth and on admission was dyspnoic (atelectasis on the right), slightly cyanotic, hypotonic, and liver and spleen were palpable 3 cm below the costal margin. Total bilirubin in venous blood was 23.75 mg%, direct bilirubin 4.9 mg%. Erythrocytes 3,340,000, Hb 10.05 g (65%), nucleated cells 90, 200, erythroblasts 610/100 leucocytes. Blood group A Rh positive, Coombs test + + +. Despite the very poor clinical condition, exchange transfusion was performed and 500 ml exchanged. The following day exchange transfusion was repeated in view of the high bilirubin level (total 37.0 mg%, direct 13.0 mg%). The infant's condition was so grave that it was possible to exchange only 350 ml. This was followed by a brief interval of clinical improvement, but on the seventh day the clinical condition markedly deteriorated, anuria developed, the liver and spleen further enlarged to 4 cm below the costal margin and became firm and hepatic foetor oris was apparent. The infant was apathetic, irritable and thermolabile. The level of both types of bilirubin, which had shown a downward trend, again rose abruptly (total bilirubin to 37.25 mg%, direct to 24 mg%). Liver function tests were normal, cholesterol 120 mg%. On the eighth day the infant appeared moribund and lay motionless, respiration was depressed, foetor hepaticus was very marked and NPN was 110 mg%. At this stage thiocapryllic acid was given in relatively large doses, the first four days 5 mg intramuscularly daily and then 10 mg alternate days three times (the average therapeutic dose is 0.075 to 0.15 mg per kg body weight). On the ninth day urine was again voided and in the following days the general condition rapidly and strikingly improved. The NPN on the 16th day was 24 mg%. On discharge at the age

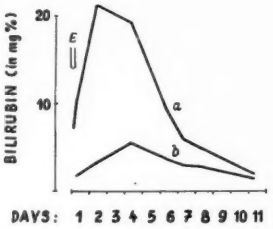


Fig. 3. a–total bilirubin, b-direct bilirubin, in the serum of full term newborn infant with a more severe form of hemolytic disease.

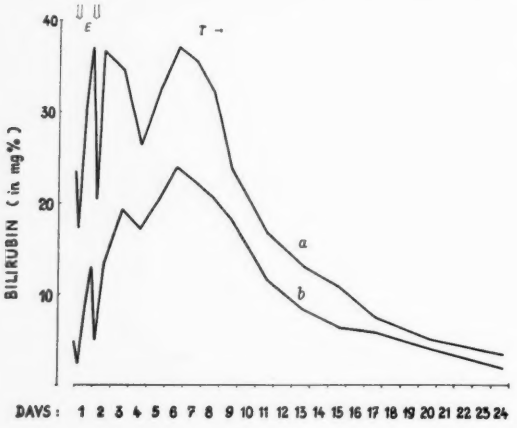


Fig. 4: a–total bilirubin, b–direct bilirubin in premature infant Ka. with very severe hemolytic disease.

of two months the infant was doing well and was neurologically apparently normal except for occasional episodes of staring gaze.

The second case involved a girl (Fig. 5) born in our hospital on 11.3.1957. She was born following the 3rd pregnancy of a B Rh negative mother, who had a high antibody titre during pregnancy. Her first child had severe jaundice after birth and died of bronchopneumonia at 4 months of age. In the second child exchange transfusion was carried out for erythroblastosis and this child is well. Our patient (2540 g, 47 cm) was B Rh-positive, cord blood bilirubin was total 9.45 mg%, direct + + + (Jendrassik-Grof method), cord Hb 4.25 g = 27%, Coombs test +, liver and spleen 3 cm below the costal margin. Exchange transfusion was carried out, 550 ml being exchanged. Despite a total bilirubin level on the 3rd day of 39.8 mg%, signs of kernicterus did not develop. Direct bilirubin was 19.4 mg%. The infant did not do well, became dystrophic, liver and spleen further enlarged to 4 cm below costal margin and an obvious caput medusae appeared on the abdominal wall. The poor general condition was

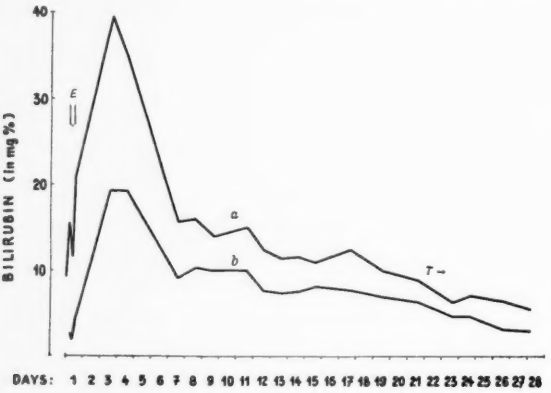


Fig. 5: a–total, b–direct bilirubin, in the serum of premature infant with very severe hemolytic disease.

further aggravated by an upper respiratory infection which developed the 3rd week. On the 22nd day, therefore, we started therapy with thiocapryllic acid, given alternate days in doses of 10 mg intramusculary until the 31st day. The liver and spleen began to diminish in size and dilatation of abdominal veins disappeared. The infant continued to improve and was discharged after 7 weeks in very good condition.

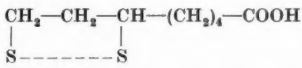
In both these cases, where thiocapryllic acid[1] was employed therapeutically for the first time, its administration was followed by striking clinical improvement. In infant Ka. it was tried as a last resort and the improvement following its use was particularly dramatic. It is not, of course, possible to draw any conclusion as to the effectiveness of this preparation on the basis of only two cases, and final evaluation of its place in the therapy of icterus gravis must await further clinical experience.

Discussion

It is well known that in hemolytic disease of the newborn indirect bilirubin is present in the blood. Direct bilirubin is usually mentioned only in connection with so-called inspissated bile syndrome. In the first days after birth, there has been little or no mention in the literature of the appearance of direct bilirubin in serum. Recently Stempfel & Zetterström (9) have studied the relation of both types of bilirubin in blood and cerebrospinal fluid. Mostly, however, the direct bilirubin has been considered negligible and routinely only total bilirubin is estimated, and assumed to consist practically entirely of indirect bilirubin.

In the light of recent studies on bilirubin one may assume that its excre-

[1] Thiocapryllic acid, recently synthetised under the name Tioctidasi at the Instituto Sieroterapico Italiano, is a substance of co-enzymatic nature, which apparently plays an important role in vivo. It is present in all organs, but chiefly in the liver. Chemically it is 6,8-dithiocapryllic acid, with the structural formula:



It is a biological catalyst, affecting many redox, acetylation and transacetylation reactions. Together with cocarboxylase, it activates oxidative decarboxylation of alpha-keto acids, and speeds the formation of "active acetate". It also affects beta-oxidation of fatty acids, oxidation of lactic to pyruvic acids, carboxylation of pyruvate to oxaloacetic, etc.

Outstanding among its therapeutic effects are (1) hepatoprotective action, (2) detoxifying action, and (3) promotion of diuresis. It has been employed primarily in liver dysfunction of all degrees of severity, from the mildest to advanced cirrhosis and hepatic coma. Its detoxifying properties have led to its use in heavy metal, arsenic and other poisonings. As a diuretic it has been reported of value in improving cardiac oedema and possibly myocardial metabolism Favourable reports have also been given of its action in disturbed motility of the intestinal and biliary tracts.

The toxicity of thiocapryllic acid is very low. It is administered either i.v. or i.m. in doses of 0.05–0.15 mg per kg per day. In hepatic coma, advanced cirrhosis or other very grave states its administration by intravenous infusion in isotonic glucose has been recommended.

tion by the liver involves two phases. In the first a chemical change in bilirubin takes place, by which indirect bilirubin is transformed to direct by conjugation with glucuronic acid with the participation of uridin-diphospho glucuronic acid. The second phase is that of excretion proper into the biliary tract.

It would seem that, from this point of view, one should distinguish between two types of hemolytic disease of the newborn. In the first, which pursues a relatively mild course, the predominating abnormality in bilirubin metabolism may be a lowered capacity of the liver to conjugate indirect bilirubin with glucuronic acid, without impairment of excretion itself. It is well known that the liver's capacity for carrying out this phase even in normal newborn infants is markedly inferior to that found in older infants and adults. With increased bilirubin production resulting from excessive hemolysis, this limited capacity may lead to accumulation of indirect bilirubin in the blood, with its concomitant danger of kernicterus. Into the second category would fall those infants in whom the course of the disease is very grave from the beginning (our two infants of low weight). In such infants one may presume that there is present severe liver damage with derangement of both components of bilirubin metabolism: conjugation with glucuronic acid and excretion from the liver. Between these two extremes one may find intermediate forms (see infant S.).

This division of icterus gravis into two types has clinical implications of some importance. If indirect bilirubin is in fact responsible for bilirubin encephalopathy in newborn infants, exchange transfusion would be indicated for infants in whom only the level of indirect bilirubin exceeds critical values (18 to 25 mg% according to various authors). Into this group would come the majority of infants with high indirect serum bilirubin and practically insignificant amounts of direct bilirubin. In such cases, as is clear from experience, exchange transfusion suffices ordinarily as the only therapeutic procedure. Adjuvant therapy in support of liver function is usually not necessary, and has not been found to be of particular value. A possibility which merits study in such cases, in our opinion, is that of employing therapeutically substances which may speed the rate of bilirubin conjugation.

In contrast, cases showing a high serum level of both direct and indirect bilirubin always require, in addition to exchange transfusion, intensive therapy in support of liver function. Whereas the first group of infants is chiefly endangered by bilirubin encephalopathy, the latter group is liable to severe hepatic damage or complete hepatic failure.

Further study of the biochemistry of bilirubin metabolism, both experimental and clinical, is of course required to confirm the views put forward here. This communication only draws attention to the possible value of

routine quantitative determinations of direct and indirect serum bilirubin in hemolytic disease of the newborn, and to certain therapeutic possibilities which present themselves, at least theoretically, in the light of recent biochemical findings.

Summary

On the basis of recent findings concerning the chemical nature of serum bilirubin, the authors recommend regular quantitative investigation of serum levels of both direct and indirect bilirubin in newborn infants with hemolytic disease. They distinguish between two forms of hemolytic disease of the newborn, the first with the predominant disturbance of bilirubin metabolism in the transformation of indirect to direct bilirubin by conjugation with glucuronic acid. The second form is presumed to involve associated impairment of the excretion of direct bilirubin from the liver. In the discussion are presented some conclusions for therapy which follow from their observations. A preliminary report is given of the results of therapy with thiocapryllic acid in two cases.

L'importance du dosage quantitatif de la bilirubine directe et indirecte dans des cas d'une affection hémolytique chez le nouveau-né.

En se basant sur des recherches récentes concernant la nature chimique du sérumbilirubine, les auteurs recommandent de faire régulièrement des investigations quantitatives de la teneur en sérum de la bilirubine directe et indirecte chez les nouveaux-nés avec une affection hémolytique. Ils distinguent deux formes d'affection hémolytique chez le nouveau-né. La première est celle avec la perurbation prédominante de la bilirubine par la conjugaison avec de l'acide glycuronique. La deuxième forme est celle dont on suppose qu'elle entraîne une diminution associée de l'excrétion de bilirubine directe du foie. La discussion renferme quelques conclusions concernant la thérapeutique, qui sont issues de leurs observations. Un rapport préliminaire a été rédigé sur les résultats d'une thérapeutique avec de l'acide thiocaprylique, appliquée dans deux cas.

Die Bedeutung der quantitativen Bestimmung von direktem und indirektem Bilirubin bei hämolytischer Krankheit des Neugeborenen.

Auf der Grundlage neuerer, die chemische Natur von Serumbilirubin betreffenden Feststellungen, empfehlen die Verfasser regelmässige quantitative Untersuchungen der direkten sowohl als auch indirekten Bilirubinspiegel im Serum von Neugeborenen mit hämolytischer Krankheit. Sie unterscheiden zwei Formen von hämolytischer Krankheit des Neugeborenen, die erste mit vorherrschender Störung des Bilirubins durch Verbindung mit Glukuronsäure. Die zweite Form schliesst, so wird angenommen, eine zugesellte Beeinträchtigung der Exkretion von direktem Bilirubin aus der Leber ein. In der Erörterung werden einige Schlussfolgerungen für die Behandlung, welche sich aus ihren Beobachtungen ergeben, dargeboten. Ein vorläufiger Bericht über die Ergebnisse der Therapie mit Thiokaprylsäure bei zwei Fällen wird angegeben.

Importancia de la determinación cuantitativa de la bilirrubina en la enfermedad hemolítica del neonato.

Fundándose en hallazgos recientes con respecto a la naturaleza química de la bilirrubina sérica, recomiendan los autores se investiguen tanto cuantitativa como regular-

mente, los niveles séricos de ambas bilirrubinas directa e indirecta en los niños recién nacidos, afectos de enfermedad hemolítica. Se distinguen dos formas de enfermedad hemolítica en el neonato, la primera con perturbación predominante de la bilirrubina en conjugación con el ácido glucorónico; la segunda, se infiere está asociada con excreción deteriorada de la bilirrubina directa, procedente del hígado. En la discussión, se presentan algunas conclusiones para fines terapéuticos, como resultado de las observaciones hechas. Casuística preliminar de los resultados terapéuticos obtenidos con ácido tiocaprílico en dos sujetos.

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CASE REPORTS

Endocardial Fibro-Elastosis

by ERNST BOYE

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Endocardial fibro-elastosis is a congenital heart disease characterized by an increase in the fibro-elastic tissue of the endocardium, most frequently accompanied by hypertrophy of the myocardium.

In most cases, the disease is associated with other cardiac anomalies, of which the most frequent are bicuspid aortic valves, hypoplasia of the aorta, foetal type of coarctation of the aorta, patent ductus arterious and mitral or aortic stenosis or atresia.

The disease has previously been described under various names, such as foetal endocarditis, endocardial fibrosis, endocardial dysplasia, and endomyocardial sclerosis.

Pathologically, the disease is characterized by considerable cardial enlargement, the weight of the heart being up to 3 to 4 times the normal average. The endocardium is greyish white and thickened; this thickening is usually most pronounced in the left ventricle and atrium, but may sometimes be generalized. The valves and chordae tendineae are often involved with polypoid vegetations on the valves. Owing to the increased work of contracting and relaxing the fibro-elastic tissue of the endocardium, hypertrophy of the ventricular musculature is almost invariably present.

Histologically, the most conspicuous feature is the increase in the fibro-elastic tissue of the endocardium. The underlying myocardium is thickened, with hyperchromatic nuclei and often with processes arising from the fibro-elastic elements of the endocardium. Inflammatory changes are absent.

The clinical picture is marked by dyspnoea, which most frequently develops in the course of a few days or weeks after the infant has been in apparently good health during the first two or three months of life. The condition becomes progressively severe, with cough, anorexia and failure to thrive. Finally, cardiac insufficiency and death occur (3, 8, 9). Of the series considered by Blomberg & Lyon comprising 25 cases followed over a five year period and 69 cases collected from the literature, 91 per cent died before the age of two years, 51 per cent within the first two weeks after

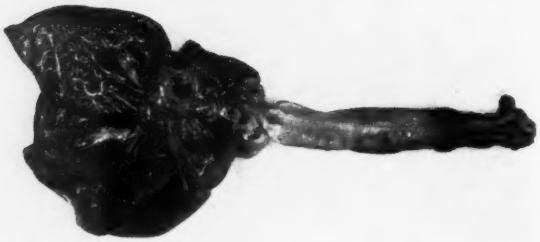

Fig. 1. The greyish white thickening of the endocardium and marked cardiac enlargement (Case 2).

the onset of symptoms, and 29 per cent within two days. Adams & Katz (1) reported that the duration of the disease varied within wide limits, ranging from sudden death to months or even years.

The diagnosis is difficult, since physical examination does not give definite information. The patients exhibit dyspnoea and permanent or intermittent cyanosis, with hepatic enlargement in slightly less than one half of the cases. Auscultation of the heart reveals cardiac enlargement and tachycardia. Cardiac murmurs, most frequently a soft systolic murmur at the apex, are present in about one quarter of the cases. The electrocardiographic findings show some variation, the most frequent abnormality being inverted T waves, which in infants are usually suggestive of congenital anomalies of the coronary arteries. Roentgen examination reveals enlargement of the heart, especially of the left side. Cardiac catheterization is no aid to diagnosis. Angiocardiography, which has been performed in a few cases (4), shows slight filling of the left ventricle during the systole and, consequently, poor filling of the aorta.

The aetiology of the disease is obscure. Inflammatory changes have never been demonstrated histologically. The occurrence in families and in enzygotic twins (11) points to a genetic factor. The disease has also been ascribed to toxic or infectious conditions in the mother during early pregnancy.

The diagnosis can only be made post mortem. No causal treatment is available.

During recent years numerous reports on endocardial fibro-elastosis have been published. The disease has attracted increasing attention, and some authors have expressed the view that it is one of the most frequent types of congenital heart disease (3). At the Children's Memorial Hospital, Chicago, it was present in 10 per cent of all cases of congenital cardiac anomalies which came to autopsy (7). In a Dano-Swedish series (4) a frequency of 2.6 per cent was reported among 1122 children with congenital heart disease. Gray (5) described a disease of adult life which pathologically seems to be

Fig. 2. Histological section showing the enormous endocardial thickening (Case 2).

similar to endocardial fibro-elastosis in infants. As only relatively few cases of endocardial fibro-elastosis have been reported from Scandinavia (2, 4, 8, 9, 10), I regard it as justified to publish the following two cases.

Case Reports

Case 1.—A boy (1592/53), born on June 21, 1953, was admitted to Hospital at the age of seven weeks. The patient was an only child. The delivery was normal and occurred about 10 days prematurely; no asphyxia, birth weight 2650 g. During the first month the infant was breast-fed, but as the mother believed that she had not sufficient milk, he was put on a 50 per cent milk formula. The appetite was poor, the baby taking only about 30 g at each feeding. He was often fretful and crying. On the day before admission he had an attack of dyspnoea and stridulous respiration.

On admission, physical examination revealed a slightly built, poorly nourished male infant with greyish cyanosis and wheezy respiration; weight 2710 g.

The heart was enlarged; murmurs were absent. Auscultation of the lungs showed no abnormalities. The abdomen was soft; there was no enlargement of the liver or spleen.

Roentgen examination revealed a large heart of globular configuration, with a strikingly narrow shadow of the great vessels and, perhaps, slight prominence of the great vessels and, perhaps, slight prominence of the pulmonary arch. A decrease in the pulmonary vascular markings was noted.

A few hours after admission the condition was further aggravated, with cyanosis and intense dyspnoea. Oxygen treatment resulted in temporary improvement, but intense dyspnoea and cyanosis persisted, and death ensued eight hours after admission.

Autopsy.—The heart was enlarged, especially in width; weight 65 g. The right atrium was somewhat enlarged and the right ventricle markedly hypertrophic. The left atrium was somewhat enlarged and the left ventricle thick-walled. The inside of the entire left ventricle was covered by a thick, fibrous whitish membrane, which made the entire wall rigid and inelastic, and fibrous bands seemed to extend into the musculature. The aortic valves were markedly shrunken and transformed into a row of small nodules, which were firm and solid to the touch and narrowed the ostium. The ductus arteriosus was widely patent, easily admitting a lead pencil. The foramen ovale was closed. Otherwise, no valvular changes were present. The aorta and the large veins around the heart were normal. The lungs showed some congestion, but were otherwize normal. Hepatic congestion, with ample blood on the cut surface, was seen, but there was no nutmeg pattern.

Case 2.—A girl (578/57), born on Dec. 23, 1956, was admitted to Hospital because of failure to thrive at the age of seven weeks. The patient was the younger of two children; her sister, aged two years, was in good health. The pregnancy had been uneventful; the mother had been under antenatal medical supervision. Delivery was normal; no asphyxia, birth weight 3350 g. The infant nursed poorly, for which reason she was put on a milk formula at the age of three weeks. The patient was supervised by a public-health nurse, who recommended a medical examination because the baby was pale, limp and failed to thrive at the age of six weeks.

On admission to Hospital, physical examination revealed a pale and slightly built female infant, weighing 3850 g. There was no cyanosis or dyspnoea on crying.

Bulging of the entire anterior thoracic wall was noted. The heart was enlarged; murmurs were absent; the pulsations of the femoral arteries were normal.

Auscultation of the lungs showed no abnormalities. There were no enlargement of the liver or spleen and no oedema.

Roentgen examination showed considerable cardiac enlargement with signs of a large left ventricle. The hilar shadows were scarcely increased in density.

The electrocardiogram showed inverted T waves in leads I and II.

During the next few weeks the infant lost weight in spite of frequent feedings. Intermittent dyspnoea and cyanosis developed, and death occurred when the infant was 11 weeks old.

Autopsy.—The heart showed considerable enlargement and dilatation; weight 115 g. The left ventricle revealed a fibrous thickening of the entire endocardium and a whitish connective-tissue mass, which formed a thick rim and disappeared irregularly and radially into the myocardium. There was slight endocardial thickening in the right ventricle and the left atrium. There were no defects of the pulmonary and aortic ostia. The mitral and tricuspid valves were perfectly normal. The coronary arteries were normally developed, and so were the aorta and pulmonary artery. The ductus arteriosus was closed; there were no malformations of the vena cava or the pulmonary vein.

Histological examination revealed considerable thickening of the endocardium, which consisted of fibro-elastic tissue with numerous elastic fibrils. There was also some increase in the fibro-elastic tissue around the larger vessels in the myocardium. From the thickened endocardium some very fine, thin and split band of fibro-elastic tissue extended into the superficial layers of the myocardium. The myocardium was markedly congested, and subendocardially there was some vacuolar myocardial degeneration. There were no signs of inflammation or myofibrosis.

Discussion

In both cases of endocardial fibro-elastosis described here the symptoms began shortly after birth with refusal of feedings, failure to thrive, later followed by symptoms of severe cardiac insufficiency. Death occurred when the infants were 7 and 11 weeks old.

In both cases, autopsy revealed characteristic greyish white endocardial changes and hypertrophy of the myocardium. Case 1 showed pronounced changes in the aortic valves and a patent ductus arteriosus. Case 2 showed no valvular changes or other congenital malformations.

Pathologically, Case 1 was similar to most other cases described in the literature. Owing to the frequent association with other cardiac anomalies, endocardial fibro-elastosis is often conceived as a condition which is secondary to these anomalies. A common explanation of the development of endocardial fibro-elastosis is that it is due to intra-uterine ventricular anoxia and disturbances in the regulation of the pressure between the coronary arteries and the ventricles caused by the accompanying anomalies.

However, this explanation is inadequate, which distinctly appears from Case 2, which showed very pronounced endocardial changes unaccompanied by other congenital anomalies.

A few cases of endocardial fibro-elastosis without involvement of the valves or accompanying anomalies have been described (3). Johnson (7) stated that no other anomalies are seen in about one third of the patients; in these patients the manifestations are less conspicuous, and they survive for longer periods. Our Case 2 shows that even in uncomplicated fibro-elastosis the changes may be conspicuous and may rapidly lead to death.

Summary

Two cases of endocardial fibro-elastosis with symptoms shortly after birth are reported. Death occurred when the infants were 7 and 11 weeks old.

In addition to endocardial fibro-elastosis, Case 1 showed pronounced changes in the aortic valves and patent ductus arteriosus. Case 2 revealed no valvular involvement or other congenital anomalies. Similar cases, which, however, seem to have been less pronounced, have previously been described in the literature.

Fibroélastose endocardiaque.

On rapporte deux cas de fibroélastose endocardiaque, dont les symptômes se sont manifestés peu de temps après la naissance. La mort est survenue lorsque les nourrissons avaient 11 semaines. Un des cas a montré, à part une fibroélastose endocardiaque, des changements prononcés dans les valves de l'aorte et dans le canal artériel de Botal inobstrué. Le deuxième cas n'a pas révélé de complication valvulaire ou d'autres anomalies congénitales. Des cas similaires, qui semblent avoir été moins prononcés cependant, ont été décrits auparavant dans la littérature.

Endokardiale Fibroelastose.

Zwei Fälle von endokardialer Fibroelastose mit kurz nach der Geburt aufgetretenen Symptomen werden angeführt. Der tödliche Ausgang erfolgte bei beiden Kindern im Alter von 11 Wochen. Einer der Fälle wies ausser der endokardialen Fibroelastose noch ausgesprochene Veränderungen in den Aortenklappen und einen offenen Ductus arteriosus auf. Beim zweiten Fall bestanden weder Komplikationen von seiten der Klappen noch andere angeborene Anomalien. Ähnliche, wenn auch anscheinend weniger ausgesprochene Fälle sind schon früher im Schrifttum veröffentlicht worden.

Fibroelastosis endocardíaca.

Dos casos de fibroelastosis endocardíaca, con síntomas manifiestos poco después del nacimiento, seguidos de muerte a las 11 semanas de edad. Además de la fibroelastosis endocardíaca, presentaba uno de los casos cambios pronunciados en las válvulas aórticas y en el conducto arterial. El segundo caso no reveló implicaciones valvulares u otras anomalías congénitas. Ya han sido citados casos similares en la literatura, aunque menos pronunciados.

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PROGRESS IN PEDIATRICS

Bronchiectasis in Children

A Follow-up Study of Surgical Treatment in Seventeen Cases

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In patients with bronchiectasis symptoms most often begin in childhood. This occurred in 80 % of Farrell's (12) and in 66 % of Ogilvie's (30) cases, and 62 % of Lindskog & Hubbell's (27) 215 cases and more than half of Gottlieb & Storm's (19) 86 cases from Rigshospitalet, Copenhagen, had symptoms before the age of 20. The latter authors found the disease to be progressive with a clear correlation between its duration and the amount of lung tissue involved.

Prognosis is generally bad in untreated or medically treated cases. Bradshaw, Putney & Clerf (5) found a mortality of 35 % among 242 patients with bronchiectasis (1941). The duration of symptoms averaged 13½ years. Twenty-six per cent of Perry & King's (33) 400 patients died. Strieder (36) found that patients who developed bronchiectasis before the age of 10 would die before the age of 40 years, but 10 % of Ginsberg *et al.*'s (18) 255 patients, 36 % of Lindskog & Hubbell's and ⅓ of Gottlieb & Storm's cases were more than 40 years at the time of operation for bronchiectasis. Both sexes are equally affected. The results of the surgical treatment will be delt with in connection with our own cases.

Aetiology and Pathogenesis

While formerly particular stress was laid on congenital abnormalities of the bronchi most authors now agree that the disease is generally aquired. Syphilis played a part in former times but is now-a-days of no importance.

Tuberculosis, especially obstruction of a bronchus from an enlarged tuberculous hilar gland, is still a factor of some importance. Jones *et al.* (24) found bronchiectasis in 70 % of 34 children in the area of former tuberculous pneumonitis (1946). Only 4 of Fiel's (13) 160 cases of bronchiectasis in children had tuberculosis.

The importance of aspiration of a foreign body is difficult to account for especially in smaller children where such an episode is often unrecognized. That the aspiration of a foreign body can very soon provoke pronounced bronchiectasis was shown by Swain & Lester (34) in a formerly healthy boy who aspirated a small screw. This could not be removed by bronchoscopy and 7 weeks later lobectomy was performed. Elaine Field (13, 14, 15), who has given the best and most detailed description of bronchiectasis in childhood, attributed none of her 160 cases to the aspiration of a foreign body and no case occurred following removal of tonsils and adenoids. Two of Buckles (6) 25 cases in children followed the aspiration of foreign bodies.

Pneumonia and pertussis are often precursors of bronchiectasis. In 56 % of Field's cases symptoms were dated from an attack of one of these two diseases (in 9 % from a combination of the two diseases). Thirty percent of Lindskog & Hubbell's and 30 % of Lorenz (28) 220 cases started after an attack of pneumonia. On the other hand bronchiectasis can not be regarded as a frequent complication in pneumonia or pertussis considering the frequency of these two diseases compared with the rather seldom occurrence of bronchiectasis. In accordance with this Biering (4) found only one single case of bronchiectasis among 151 children who had been hospitalised for pneumonia (66 of them for pertussis-pneumonia). Bronchography was only made however in the two patients where the history was suspicious.

The importance of atelectasis with the characteristic triangular shadows on the chest roentgenograms was emphasized by among others Anspach (1), Biering (3) and Field (14). The latter author found irreversible bronchiectasis in 42 % of 272 children with pulmonary collapse, and pulmonary collapse in 46 % of 160 children with bronchiectasis. If the collapse and the cough is not diminishing in the course of 3 months there is great danger of bronchiectasis to occur. When the alveoli are collapsed the inspiratory forces will tend to dilate the bronchi.

The combination of bronchiectasis and asthma is not seldom at all. One third of Field's 160 patients had present or former symptoms of asthma. Half of Laursen's (25) 73 grown-up patients with bronchiectasis had asthma as their major symptom. Overholt *et al.* (32) found bronchiectasis in 35 % of 76 patients with severe asthma, Hovesen (23) in 29 % of 75 asthmatics, while Westermark & Wiholm (39) only found 4 % in 100 patients with asthma. Warringa (38) found at least 2 positive characteristics of allergy in half of 227 cases of bronchiectasis. All these series seem only to be composed of adults.

Sinusitis can be demonstrated in a high percentage of children with bronchiectasis. Field found roentgenologic evidence of sinus infection in 85 % of 142 examined cases. Antral puncture was done in 100 of these cases. Eighty per cent showed mucopus in the washouts. The connection between sinusitis and bronchiectasis is not clear. Secretions from the nasal sinuses can drip into the bronchi. Alternatively the nasopharynx can be infected from coughing-up of bronchial secretions. Generally the sinusitis disappears after surgical removal of the bronchiectasis.

Situs inversus can be seen together with bronchiectasis and sinusitis (Kartagener's triad). Field had none of these cases in her series, while 3 of Lindskog & Hubbell's 215 patients had this anomaly. Bergstrom *et al.* (2) have described familiar occurrence of this syndrome. Other congenital malformations were found in 4 of Field's 160 cases.

Finally bronchiectasis is often seen in cases of cystic fibrosis of the pancreas. Pronounced bronchiectasis and alterations of the lungs in connection with the characteristic microscopic appearance of the pancreas were found in 6 infants dying between the age of 2 and 11 months in the pediatric department of the Rigshospital. In 2 of

these cases, who died shortly after admission, the diagnosis was only made after microscopic examination of the pancreas. This investigation is thus important in similar cases.

Symptoms

No detailed description of the symptoms is intended here. Constant cough is the most frequent symptom, while sputum is missing in the smaller children who swallow it. Haemoptysis is not a common symptom in children. It occurred in 7 % of Field's cases and was the main symptom in 12 % of Lindskog & Hubbell's patients, but in other series it appeared in one third of the cases or more. Underweight, chest deformities and clubbing is usually present in severe cases. Repeated attacks of pneumonia should always give suspicion of bronchiectasis. Even in quiet periods, with no symptoms of bronchitis, moist rales can often be heard over the affected area especially during inspiration after coughing. Laboratory tests (sedimentation rate, blood count) are only of minor importance in assessing the severity of the disease. Bacteriological examination including the search for tubercle bacilli and the determination of the resistance against antibiotics should always be done. Bronchoscopic aspiration of secretion is often necessary.

Diagnosis and Localization

The diagnosis must always be confirmed by bronchography. The technique of this procedure has been described by Gudbjerg (20). Ordinary chest roentgenograms will in most cases give suspicion of the disease. Thus Gudbjerg (21) found completely normal roentgenograms in only 7 % of verified bronchiectasis. His series is mainly composed of severe cases in adults. In all the surgically treated cases the bronchographic diagnosis was confirmed by examination of the removed part of the lungs (21, 22). In all published reports the disease was most commonly located to the left lower lobe. This lobe was injured in no less than 85 % of Field's 160 cases. In 65 % of her cases the lingula was involved, in 62 % the right middle lobe, in 54 % the right lower lobe, in 30 % the right upper lobe, and in only 24 % the left upper lobe was involved. The reason why the lower lobes are so frequently affected is that the disease has a predilection for lobes whose bronchi are directed upwards against gravity. In about one third of Lindskog & Hubbell's cases the disease was unilobar, in about one third it was multilobar but unilateral, and in the last third it was multilobar and bilateral. Warringa (38) found that no less than 46 % of his 282 cases were bilateral.

It is of great importance that bronchiectasis can be reversible (Field (13, 14), Lees (26), and others). In doubtful and less severe cases continued observation with repeated bronchograms should therefore be done before the decision of operation is taken. On the whole the tendency presumably rather goes in the direction of omitting bronchography and surgery in proper time.

Personal Investigations

The material consists of 17 children who were between 5 and 15 years old at the time of operation for bronchiectasis. The operations were performed in the years 1947–1956 in the department of thoracic surgery of the Rigshospital, Copenhagen. Sex and age distribution (at the onset of symptoms—and at operation) is shown in Table 1.

TABLE 1

Age and sex distribution at the onset of symptoms and at the time of operation for bronchiectasis.

	Age (years)				
	0–1	1–3	4–10	11–15	Total
At onset					
Boys	3	2	3	0	8
Girls	3	4	1	1	9
Total	6	6	4	1	17
At operation					
Boys	0	0	7	1	8
Girls	0	0	2	7	9
Total	0	0	9	8	17

In this rather small series the boys were operated at an earlier age than the girls although the latter generally had symptoms from the earliest time of life. As will be shown later the best results were obtained among the boys.

Aetiology

Prematurity occurred in 3 cases (weight at birth between 1500 and 2250 g, in 3 cases birth weight is unknown). Social conditions: 8 children lived under definitely bad social conditions, 4 came from good homes, and 5 from fairly good conditions. The proportion of children from very bad social environments is higher than that generally seen in this hospital.

Eight of the parents dated the onset of symptoms from an attack of pneumonia, and 8 children had had repeated episodes of pneumonia. In 2 cases the disease seems to have started after pertussis. In all 8 of the children had had pertussis, 7 had not contracted this disease, and in 2 cases it could not be determined if they had had it or not. In one girl the disease originated from pulmonary tuberculosis with swelling of the right hilar lymph-nodes at the age of 3 years. Subsequently atelectasis of the right lower and middle lobes occurred, but tubercle bacilli were not found during the last 8 years before lobectomy was performed. In no case a history of aspiration of a foreign body or the beginning of symptoms after tooth extraction or removal of tonsils or adenoids was obtained.

Signs

An almost constant cough was present in all cases. Eleven of the children had sputum, but in only one the sputum was foul-smelling. Haemoptysis

occurred in 3 cases, in one of them as the first symptom. Dyspnoea after heavy exercise was noted in 6, and pain in the chest in 3 instances. Two had asthma but in a rather mild form. Twelve had recurrent attacks of fever, 8 of which were considered real attacks of pneumonia. Two children had pleurisy before operation. Eight had clubbing of the fingers, generally only in a mild degree.

Associated Disease

One child had paresis veli palatini of unknown origin; 1 cheilo-gnato-palatoscisis which had been operated at 2 months and at 2 years; 1 boy had cirrhosis hepatis with symptoms from the age of 2 years. He had already had 3 attacks of pneumonia at that time. At the age of 5 left lower lobectomy and lingulectomy was performed. He is now 13 years old and doing well, although some ascites is present at intervals. Finally a fourth child had had an acute encephalitis with hemiparesis 4 years before he got symptoms of bronchiectasis.

Localization and Extension

In 7 cases the disease was located to the right side alone, in 8 to the left side, and in two cases the disease was bilateral.

Right side		*Left side*	
lower lobe	1	lower lobe	1
middle lobe	2	lower lobe and lingula	6
lower and middle lobes	2	whole left lung	1
middle and upper lobes	1	Total	8
whole right lung	1		
Total	7		

Bilateral

left lower lobe and lingula + right middle lobe	1
left lower lobe and lingula + right lower lobe	1
Total	2

In 4 patients the disease was unilobar, in 11 multilobar but unilateral, and in the remaining two multilobar and bilateral. The lingula has here been numbered as a lobe.

Roentgenologic Changes

A detailed description of the radiological changes on the plain chest film and bronchogram in bronchiectasis and the pathological basis of these

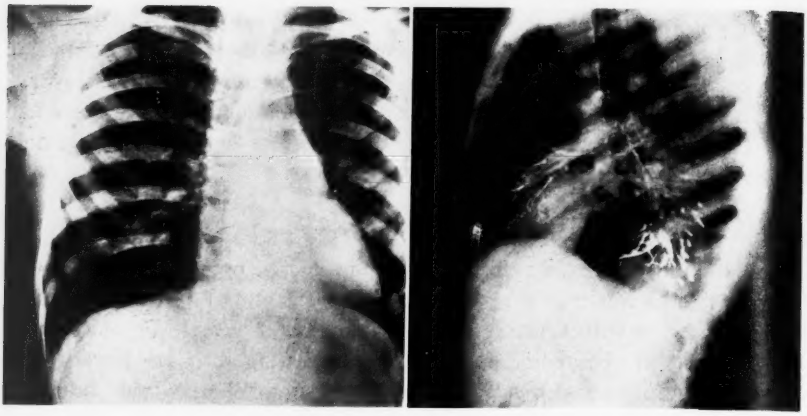

Fig. 1. Boy, aged 10. (*a*), *left*: Frontal view. Triangular atelectasis of left lower lobe (visible through the heart), otherwise normal pulmonary markings. (*b*), *right*: Bronchogram: Cylindric bronchiectasis in left lower lobe. Confirmed by operation.

changes has been discussed in a previous publication by one of us (Gudbjerg (21)). The changes found on the plain films were increased lung markings, honeycomb-like structure, atelectasis or pleural adhesions. In a series of 112 patients increased lung markings were demonstrated in 85%. Honeycomb-like structure was less common, being distinct in only 24%. Total or lobar atelectasis was present in 31%. The nature of the changes does not differ from the findings in adults. There is, however, a characteristic difference in the incidence of the demonstrable changes.

Thus in our material consisting exclusively of children lobar atelectasis was found in 11 cases (64, 7%), 6 of these presenting the characteristic basal triangular type, which was first described in detail by Warner & Graham (37) in 1933 (see Fig. 1.).

Typical honeycomb-like structure was found in 2 cases, and both these patients had saccular dilatations in the left lower lobe and lingula.

Greatly increased lung markings were demonstrated in two patients, slightly increased in one, whereas in one case the lung markings were normal. Bronchographic examination afforded information about the nature and extent of the dilatations with great certainty. Comparison between bronchogram and operative findings thus revealed good conformity. In 10 patients the dilatations were cylindrical, in 3 saccular, and in 4 there was a combination of the two types.

While negative radiographic findings do not exclude the presence of bronchiectasis, positive findings afford great diagnostic aid, when combined

with the clinical symptoms. It must be pointed out, however, that a definite diagnosis requires bronchographic examination which is also the only means of establishing the nature and spread of the dilatations.

Treatment

All patients were treated with breathing exercise and postural drainage, and all had treatment with penicillin after and often before operation. In a few cases other antibiotics were also given. Bronchoscopic aspiration was used when indicated.

Twenty-two operations were performed upon the 17 patients. One patient had three operations. First: left lower lobectomy, the other parts of the lung looked normal. Second: lingulectomy 13 months later. After this operation complete collapse of the remaining upper lobe occurred. Despite suction the atelectasis persisted. Third: left upper lobectomy 7 weeks later. Three patients went through two operations each. Only one patient was operated on both sides. In one patient bronchiectasis in the left lower lobe was overlooked on the bronchogram. Thus 7 months after lingulectomy, since the symptoms persisted, left lower lobectomy had to be done. The third patient who underwent 2 operations had right lower and middle lobectomy at the age of 8 years. Pneumonia supervened in the remaining upper lobe 10 days after the operation but was cured with penicillin. She did well for 2 years when a new attack of pneumonia resulted in complete collapse of the right upper lobe, which was removed 5 months later.

In the remaining 13 patients the removal of one or two affected lobes was performed in one séance. Two of the patients had pneumonectomy, but this was done through 3 respectively 2 operations as described. In only one case the method of mass ligation (tourniquet method) was employed, in the other patients the dissection method was used.

Postoperative Complications

There was no hospital mortality. The following postoperative complications occurred: Atelectasis, 7; pneumonia, 1; empyema, 1; haematoma, 1; bronchial fistula and other complications, 0.

The haematoma and the empyema occurred in the same patient, namely the one in which the tourniquet method was employed. This patient was well at the time of follow-up 7 years after the operation. The atelectasis was only pronounced in one patient. The course of events in the patient with total atelectasis in the remaining upper lobe and in the patient with pneumonia has already been described. In the other patients the atelectasis was small and subsided in the course of one or two weeks. All these patients were well at the follow-up.

Late Follow-up Results

All patients were examined several times after the operation. The period of observation ranged between 12 and 87 months (1 and 7¼ years) and averaged 51 months (4¼ years). One patient died 17 years old, i.e. 4 and 1½ years, respectively, after left lower lobectomy + lingulectomy and right middle lobectomy. There had been no complications postoperatively but she had about 25 attacks of pneumonia after the first operation. A bronchogram 15 months after the second operation showed development and progression of postoperative bronchiectasis on both sides (see Fig. 2.). She died 3 months later of pneumonia.

Among the remaining 16 patients 12 were completely free of symptoms tolerating the same amount of exertion as their mates. Four were much improved with only minor symptoms persisting such as fatigue and dyspnoea following heavy exercise or a little cough and sputum. None of the patients were unchanged or worse. Some of them had had a certain amount of dyspnoea and scoliosis for a year or so after the operation.

In two of the patients who were improved but not symptom-free pneumonectomy had been performed. None of the improved cases had any important postoperative complications, but in one of them the patient had a slight fever for about 2 months after the operation. In 3 of the 4 improved patients bronchography disclosed remaining or new dilatations. The best results were obtained in the boys: Only one of the 8 boys was not symptom-free at the follow-up, whereas one of the girls had died, and three had persistent symptoms.

Postoperative Bronchography

This examination was done in 12 of the 17 patients. The findings in the patient who died has been described above. Among the remaining 11 patients no bronchiectasis was found in 7, in all of whom the clinical result was excellent. In an additional patient, who was also well at the follow-up, a few new dilatations were seen on the bronchogram on the operated side. The remaining three patients were not free of symptoms and in all of them bronchography showed bronchiectasis. In one the operation had not been radical and some bronchiectasis had been left behind; in the two other patients new small dilatations had developed on the non-operated side.

In 5 cases no postoperative bronchography could be obtained. The ordinary chest roentgenograms were normal in 4 of these patients, three of whom were clinically well, while the fourth had a little dyspnoea on exertion. The fifth patient had bilateral bronchiectasis but only unilateral operation. She is doing well 2½ years after operation although the chest roentgenograms

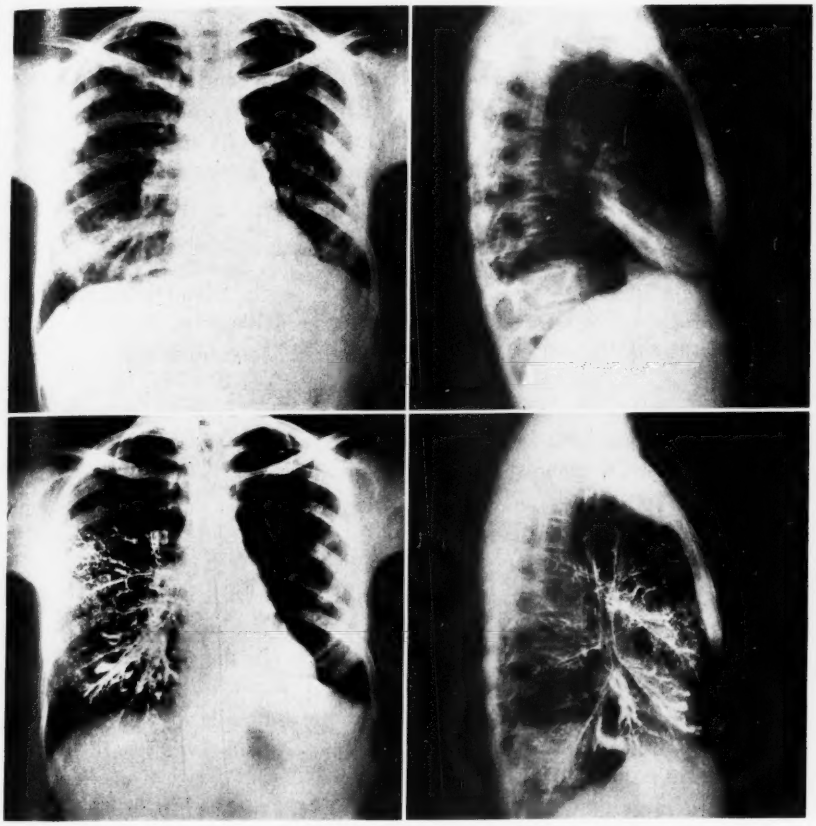

Fig. 2. Girl, aged 15. (*a*)–(*b*) Ordinary chest roentgenograms show sequelae of left-sided thoracotomy, performed two years previously, when the left lower lobe and the lingula were removed for cylindrical bronchiectasis. The right side reveals slightly increased pulmonary markings, slight pleural changes and a partially atelectatic middle lobe. (*c*)–(*d*). Bronchograms: Cylindric and saccular bronchiectasis in right middle lobe and anterior segment of right lower lobe. Confirmed by operation.

are suspicious of remaining disease on the non-operated side. Apart from this exception good correlation between less satisfactory clinical result and remaining or new bronchiectasis was found in our cases. On the other hand, we observed that the development of small postoperative dilatations did only compromise the result of the operation to a small extent.

Comparison of Duration and Extent

In the 4 patients with only one lobe affected the duration of symptoms averaged 4.5 years. In 11 cases with two lobes involved the duration was

on an average 6.4 years, and in the two cases with three lobes attacked it was 10.5 years.

The duration in the boys was on an average 5.4 years, whereas it was 8.2 years in the girls. In the boys on an average 1.6 lobes were involved, while in the girls the average was 2.1 lobes. This seems to be a good explanation for the better results among the boys. A correlation between the duration and the extent of bronchiectasis was also found by Gottlieb & Storm (19).

Discussion

Meade, Kay & Hughes (29) had only one operative death in 160 patients on whom 196 lobectomies were performed. The operative mortality in Lindskog & Hubbell's (27) series was 2.9%. Sixty-nine per cent of the operated patients were cured or much improved, compared with only 12.7% in the non-surgical group. Ochsner *et al.* (31) had no hospital mortality on their last 92 operations, and the mortality from the lung disease was 3.1% at follow-up. Seventy-seven per cent of the patients were cured or had only minor symptoms. Buckles (6) had no mortality at all among 25 children with an average age of 7 years at operation. Sixty-four per cent were symptom-free at the follow-up and all were better than before operation. He does not mention the length of the follow-up period. Field (15) had a mortality of 9.7% in 93 operated children. In the group with asthma (31 cases) the mortality was 16%, whereas it was 6.4% in those without asthma. The prognosis in 36 cases who underwent bilateral operation did not seem to be less favourable than that found in the cases treated by unilateral resection.

Ginsberg *et al.* (18) had good results in 75% of 221 operated cases of bronchiectasis, whereas 4% had died. The results were often bad when the patients had severe postoperative complications or remaining dilatations. Thirty of their patients were children (Cooley *et al.* (9)). Among these the result was only good in 60 %. The reason for this was thought to depend on unsatisfactory coughing-up of secretions in the operated children. In such cases the authors recommend tracheotomy and bronchoscopic suction postoperatively. On the contrary Edwards (11) had the best results when the patients were operated before the age of 20. This is seen in Table 2.

The importance of the age of the patient and of the length of the period of observation is clearly seen. Edwards mentions that the postoperative mortality rate fell from 5% to below 1 % among his cases from Liverpool.

The results in our own small series are comparable with the best published hitherto.

Supportive treatment with antibiotics, breathing exercise, postural

TABLE 2

Follow-up of surgical treatment for bronchiectasis (from Edwards).

Period of observation (years)	Age (years)	Number of patients	Good result %
3–5	0–19	84	69
5–9	0–19	74	58
3–5	over 20	66	44
5–9	over 20	75	39

drainage and sometimes bronchoscopic aspiration is most important as well as a good teamwork between pediatricians, thoracic surgeons, radiologists anaestesiologists, physiotherapists and nurses.

Prophylaxis primarily consists in the prevention and active treatment of pneumonia, pertussis, atelectasis and chronic bronchitis. Prolonged convalescence with breathing exercise and postural drainage is necessary when symptoms persist. When bronchiectasis is irreversible surgical removal is advocated.

Summary

The literature concerning bronchiectasis especially in children is reviewed. Aetiology, symptoms, localization etc. in our 17 cases is reported. In 8 cases the disease started after pneumonia and in two after pertussis. Prematurity occurred in 3 of the children. Eleven had signs of atelectasis on ordinary chest roentgenograms. On an average the disease was most extensive in the cases of the longest duration. All patients were treated with lobectomy.

At the time of follow-up, which averaged 4 ¼ years, 12 patients were symptom-free, 4 improved, and one patient had died. This was the only child who had bilateral lobectomy. A postoperative bronchogram showed formation of new bronchiectasis and she had repeated attacks of pneumonia. In 11 other cases postoperative bronchography revealed no bronchiectasis in 7, formation of new dilatations in 3, and remaining bronchiectasis in one. In 3 of the four patients with persisting symptoms dilatations were found by bronchography.

The surgical removal of bronchiectasis in children is highly recommended, unless the disease is too widespread, since the prognosis is far better after operation than without. It is hoped that follow-up examinations 15–20 years or more after operation or medical treatment will be published so that the final prognosis can be established.

Bronchectasie chez des enfants. Etude sur le résultet d'un traitement chirurgical dans 17 cas.

On rapporte l'étiologie, les symptômes, la localisation, etc., constatés dans les 17 cas. Dans 8 cas, la maladie a commencé après une pneumonie, et dans 2 autres, elle s'est manifestée après une coqueluche. Chez 3 enfants, une prématurité est survenue. Onze enfants ont eu des indices pur une atélectasie, en faisant des radiogrammes ordinaires

de la poitrine. En moyenne, l'affection a été la plus étendue dans les cas qui ont duré le plus longtemps. Tous les malades ont été soumis à une lobectomie. Pendant la période que les malades ont été suivis, durant 4 ans et demie environ, 12 d'entre eux n'ont plus manifesté de symptôme, 4 autres se sont améliorés, et un seul a décédé. Cette enfant est la seule qui ait subi une lobectomie bilatérale. Un bronchogramme postopératoire a démontré la formation d'une nouvelle bronchectasie et elle a eu des crises répétées de pneumonie. Dans 11 autres cas, la bronchographie postopératoire a révélée que 7 d'entre eux n'ont pas eu de bronchectasie, 3 malades ont démontré une formation de dilatations nouvelles, tandis qu'une bronchectasie permanente a été constatée dans 1 cas. Parmi les 4 malades avec des symptômes persistants, on a trouvé par bronchographie la présence de dilatations chez 3 d'entre eux. A moins que l'affection ne soit trop étendue, une suppression chirurgicale de la bronchectasie chez des enfants est à recommander au plus haut point, puisque le pronostic est beaucoup mieux après une opération que sans celle-ci. On espère qu'après 15–20 ans ou plus tard, les examens suivis seront publiés, afin que le pronostic final puisse être établi.

Bronchiektasien bei Kindern. Eine Nachuntersuchung von 17 chirurgisch behandelten Fällen.

Bericht über 17 Fälle mit Angabe von Aetiologie, Symptomen, Lokalisierung u.s.w. Bei 8 Fällen setzte die Erkrankung nach Pneumonie und bei 2 nach Keuchhusten ein. Drei von den Kindern waren Frühgeburten. Elf wiesen auf gewöhnlichen Roentgenbildern der Lungen Zeichen von Atelektase auf. Die Erkrankung war im Durchschnitt am stärksten ausgedehnt bei Fällen mit längster Dauer. Alle Kranken wurden lobektomiert. Zur Zeit der Nachuntersuchung — durchschnittlich 4½ Jahre nach der Operation — waren 12 Kranke symptomenfrei, 4 gebessert und eine tot. Dieses war das einzige Kind, bei dem beidseitige Lobektomie durchgeführt worden war. Auf einem postoperativen Bronchogramm konnte erneute Formierung von Bronchiektasien nachgewiesen werden und sie hatte wiederholte Anfälle von Pneumonie. Unter elf anderen, mit Hilfe von Bronchographie postoperativ untersuchten Fällen zeigten 7 keine Bronchiektasien, 3 Formierung neuer Dilatationen und einer ein Fortbestehen der Bronchiektasien. Bei 3 unter den 4 Kranken mit andauernden Symtomen wurden mit Hilfe von Bronchographie Dilatationen festgestellt. Chirurgische Entfernung von Bronchiektasien bei Kindern wird warm empfohlen, wenn die Krankheit nicht allzu ausgedehnt ist, da die Prognose nach Operation viel besser sei als ohne sie. Die Hoffnung wird ausgesprochen, dass Ergebnisse von weiteren Nachuntersuchungen nach 15–20 oder mehr Jahren veröffentlicht werden werden, um die endgültige Prognose sicherzustellen.

Bronquiectasia infantil. Estudio sistemático del tratamiento quirúrgico en diecisiete casos.

Casuística de la etiología, síntomas, localización, etc., en diecisiete enfermos. En ocho casos, se declara la enfermedad a consecuencia de neumonía. En dos otros casos, aparece después de pertussis. Prematuridad en tres de los niños. Once con síntomas de atelectasia en los roentgenogramas pectorales ordinarios. De un modo general la enfermedad presenta una mayor extensión en los casos de más larga duración. Todos los pacientes están sometidos a lobectomía. Durante la observación sistemática, durante unos 4 años y medio, se declaran 12 pacientes exentos de síntomas, 4 mejorados y uno muere. Esta ultima niña fué la única sometida a lobectomía bilateral. Un bronquiograma postoperatorio revela la formación de una nueva bronquiectasia, manifestándose ataques repetidos de neumonía. De los otros 11 niños, en 7 de los casos, la bronquio-

grafía postoperatoria no revela la existencia de bronquiectasia y en 3 casos aperece la formación de nuevas dilataciones, con un caso de bronquiectasia prevaleciente. En 3 de los 4 pacientes con síntomas persistentes, la broncografía revela dilataciones. Se recomienda eminentemente la escisión quirúrgica de la bronquiectasia infantil, reservado el caso de estar la enfermedad demasiado difundida, ya que, el pronóstico es mucho más favorable después de la operación que sin ella. Se confía que la observación sistemática después de 15 a 20, o más, años, sea publicada oportunamente, con objeto de poder determinar el pronóstico final.

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BOOK REVIEWS

Gertrud Soeken: **Kernikterus und Morbus haemolyticus neonatorum.**

Ferdinand Enke Verlag, Stuttgart, 1957.

This monograph is based on a clinical survey of 174 children with hemolytic disease of the newborn, 137 of these surviving the newborn period. The author's main interest has also been to study the histopathological aspects of the brain damage occurring in kernicterus, and autopsy material has been investigated in detail, using conventional histological technique. The author claims that the changes of the brain in kernicterus are primarily due to a developmental injury of the brain cells in the basal ganglia, occurring already during fetal life. This injury is thought to be caused by tissue hypoxia. The yellow staining produced by bilirubin entering into the brain tissue is regarded as a secondary phenomenon, being of questionable importance. Recent experimental work, however, strongly indicating the toxic action of indirect bilirubin is almost overlooked and only briefly discussed. This toxic effect, whether it is combined with a previous nerve cell damage or not, can be greatly reduced by the use of repeated exchange transfusions, as indicated by daily estimations of indirect bilirubin levels. The author's experience as to the value of exchange transfusion is based upon single transfusions, frequently performed too late. It is unfortunate that the histopathological findings in her material have led to false conclusions concerning the value of modern treatment of an erythroblastotic child. The consequences of such a therapeutic nihilism are reflected in the high incidence of fatalitites and neurological sequelae in the material as compared to the results achieved in leading centers, where the principles of repeated exchange transfusions have been adopted.

Bo Hellström, Stockholm

L. T. Hillard and Brian H. Kirman: **Mental Deficiency.**

J. & A. Churchill Ltd. London. 1957. 517 pages, 90 figures. Price 60 shillings.

This book is the product of a team of workers in the field of mental deficiency who have specialized themselves in different aspects of the work. Hillard, Kirman and Crome are members of the Consultant Staff of the Fountain Hospitals in London, O'Connor and Tizard are members of the Brit. Med. Research Council Social Psychiatry Research Unit, Elizabeth Williams has been Supervisor of the Hanworth Special Training School. The emphasis is placed on the social and clinical aspects of the problems rather than on the old theory of impaired germ plasm. This is a more constructive approach, because it is always possible to alter an individual's environment, while it is too late to alter his genetic inheritance. Part I deals with the background of mental deficiency. It is stated that the precise cause and pathogenesis of the great majority of cases of mental deficiency remains unknown. The incidence of mental defectives in England and Wales in 1954 was 3 in 1000 of the population. Social factors, relevant to the causation of mental defects, are dealt with. Our present knowledge of the general morphological and gross and histological substrate in mental deficiency is reported as well as the pathology of certain syndromes. The classification of mental defectiveness is discussed at some length and the British system mentioned (feeble-minded 50–69, imbecile 20–49, idiots 0–19 I.Q. range). The methods of measurements of intelligence and the validity of such tests is discussed. In part II the mentally handicapped individual is described, the assessment of the defect, the educational problems in children of school age and the social problems of adolescents and older defectives. Special chapters are devoted to the physically handicapped, mentally deficient child, to cerebral palsy, deaf and blind children etc., and to more detailed clinical description of mongolism, errors of metabolism, endocrine disturbances and morphological changes and lesions of the brain and the skull as causes of mental deficiency. In part III the authors write on care, education, training and treatment of mentally deficient children. "Advice to parents" is an interesting and enlightening chapter. Although the book takes special consideration of English conditions and legislation, it gives sound knowledge of all problems inherent in mental deficiency of interest for the physician in all countries. A series of references after each chapter increases the usefulness of the book.

W. C. Davison: **The Complete Pediatrician.**

Duke University Press, Durham, N.C. 1957. Price $ 4.25.

This book resembles no other book on medical matters. The author characterizes it truthfully that it, with its numerous cross reference numbers, resembles a telephone book or mail order catalogue. It is a reference book representing an effort to compile and condense those practical pediatric facts which, though essential, usually slip from memory. It will relieve the pediatric practitioner of the nuisance of hunting for data in several books and periodicals. When the instructions for its use has been carefully read and after some experience it will show itself to be very useful. It is well known all over U.S.A. by practitioners and pediatricians, and that it is well appreciated can be judged by the 45,000 copies that have been sold of the earlier 6 editions. It puts emphasis on symptoms, signs, and physical and differential diagnosis and may therefore be of more practical value than a systematic text-book. The symptoms and diseases have been divided into seven chapters on the basis of anatomical system chiefly involved, and each chapter contains description, laboratory tests, differential diagnosis,

treatment, prognosis and prevention. Other chapters deal with detailed description of how to perform mentioned laboratory tests, general measures of treatment, growth, development and child psychiatry, recommended drugs and prescriptions. The book is written with good humor and is an excellent assessment of our present knowledge in the field of pediatrics. It can be warmly recommended as a quick reference book to students, practitioners and pediatricians. May Dr. Davison and his family-members–collaborators get the money from the sale of the book enabling them to do more traveling, one of the reasons he mentions for the printing of this new edition.

H. Opitz and B. de Rudder: **Pädiatrie. Ein Lehrbuch für Studierende und Ärzte.**

Springer Verlag. Berlin-Göttingen-Heidelberg. 1957. Twelve hundred and twenty pages, 527 figures, numerous tables. Price DM 78.

In the preface this book is presented as a textbook *and* reference book. It is printed with small types and there is a frequent use of petit-print. The book may almost be regarded as a minor successor of the well-known Pfaundler-Schlossmanns Handbook of Pediatrics. It is without doubt too voluminous for medical students, but as a reference book it gives a lot of useful information. It is of interest for the reader to assess how the teachers of pediatrics in the West-Germany of to-day look at various problems regarding child health. It is of course not possible to enter into a detailed judgement of each chapter. The general impression is that the authors in a masterly way have covered their subjects. The following comments may be made. Rheumatic fever is described in the same chapter (Rheumatosen) as rheumatoid arthritis and periarteritis nodosa, and in the differential diagnosis of cases of rheumatic fever starting with polyarthritis only osteomyelitis, acute leukemia and growing pains are mentioned. Apparently all other kinds of acute polyarthritic pains even without any clinical affection of the heart, are regarded as rheumatic fever. In the chapter on Blood the determination of the life span of the erythrocytes by radioactive chromium is not mentioned. The amount of hemoglobin is still recorded in per cent of the normal, not in gram-per cent. A discussion on the prophylactic value of chemotherapy in tuberculosis-infected infants and small children would have been valuable, as direct therapeutical influence on the lesions of primary tuberculosis is rather dubious. It is surprising that retrolental fibroplasia is almost unknown in Germany. A great number of the figures are colored, and in most of them the color is adequate, but in many there is a too pronounced yellow tint. In some big tables various types of tumors in childhood are listed. Common intoxications with therapy, drugs and prescriptions used in pediatrics are also given and they are very informative and will certainly be much appreciated by German physicians. The book ends with a reference list covering 21 pages, mostly German books and periodicals. The editors of this book, Opitz and de Rudder, who have also themselves written some of the best chapters, as well as the publisher are to be congratulated for this fine book that so well reflects the present high standard of pediatrics in Germany.

Paul Gegesi Kiss: **Das Koma und seine Behandlung bei Diabetes Mellitus im Kindesalter.**

S. Karger. Basel, New York, 1956. 86 pages, 21 figs. Price Sw. fr. 11.90.

In spite of the present knowledge and modern trends in the treatment of diabetic coma, the role of coma-death in the mortality of diabetic children seems to be important

at several clinics in the world—also at those, where "one knows how to treat diabetes". The author offers detailed guidance in the description of the different types of diabetic coma, and most valuable is the attention he pays to the atypical, paradoxical forms without hyperglycemia and or without acetone bodies in the urine. In the first type it might be an "insulin-ketosis" or a ketosis due to the lack of carbohydrates. To exemplify the second type the author describes a patient, who died in coma and in whom the autopsy revealed regressive changes in the pituitary gland and a fatty liver—the stimulus and the place of the origin of acetone bodies respectively. The author introduces a new idea—that of the terminal stage, which means that stage where the changes due to the coma have become irreversible. In the treatment the author mainly follows the principles accepted everywhere in the world. The importance of an initial high dose of insulin, followed by repeated smaller doses during the first 24 hours, is stressed. Still, I think the suggested doses of 10–30 units intravenously are too small. The Joslin school recommends 50–100 units, partly intravenously, and according to my experience the risk of hypoglycemia is very small if one pays attention to the contemporary and consequent restoration of the dehydration and loss of electrolytes, these being the most important clinical features of diabetic coma. The author points out the importance of giving fluids with electrolytes—Ringer—in the first hand and alkalies in the second. The question is whether the use of alkalies is not quite needless—or may even be harmful. I refer to Falta, who mentions that alkaline solutions given intravenously may check diuresis and lead to insulin edema. As a good review of the problems of diabetic coma in children this book will be recommended to pediatricians interested in diabetes and metabolic disorders.

Lars Ström, Stockholm.

ANNOUNCEMENTS

International Children's Centre.

Courses to be arranged in 1958: Course on day and residential nurseries: January 6–January 26. Course on mentally defective children: January 27–March 2. Course of social pediatrics (Dakar): February 24–April 4. Course on tuberculosis in the child (in French and in English): March 3–March 30. Course of social pediatrics: April 14–July 5. Course on nutrition: September 15–October 12. Course on maternal and child welfare for social and administrative personnel: October 13–December 20. Maternal and child welfare training course for African midwives (Dakar).

The Guigoz Scholarship on Nutrition.

The Jury charged to award the Guigoz scholarship for 1957–1958, retained the applications of Doctors D. Petrovic (Belgrade) and H. Kâser (Berne) at its meeting of July 1st, 1957. The two scholarship holders will begin their research work in the autumn,

at the research centre on child nutrition, under the guidance of Professor P. Royer (Paris).

For the year 1958–1959, the Guigoz scholarship will be awarded by the International Children's Centre. The applicants should send to the International Children's Centre, Château de Longchamp, Bois de Boulogne, Paris XVI°, *not later than May 15, 1958*:

(a) *a curriculum vitae* listing their studies on biological and social problems pertaining to nutrition or to infant and child feeding,

(b) *a letter of introduction* from one of their masters,

(c) *a statement on the studies* they wish to pursue with the help of the Guigoz scholarship.

The applicants must command an adequate knowledge of the French language. At the conclusion of their scholarship period the scholars will be expected to send to the International Children's Centre a *scientific paper* on the subject they will have studied during the year.

The Twelfth Northern Pediatric Congress.

This Congress will be held in Helsingfors, June 29th to July 2nd 1958. Professor C. E. Räihä is President and Professor N. Hallman is General Secretary. Three main subjects will be discussed: *perinatal mortality and its prophylaxis, etiology of disorders of the urinary tract*, and *factors influencing the somatic development of children*. The address of the Organization Committee is Stensbäcksgatan 11, Helsingfors, Finland.

European Organization for Research on Fluorine and Dental Caries Prevention.

The 5th Congress of the *European Organization for Research on Fluorine and Dental Caries Prevention* will take place in Brussels from May 30th to June 1st, 1958, in connection with the Brussels Universal and International Exhibition. The main themes of the congress will be: (1) The physiologic effect of small doses of fluorine; (2) Radioisotopes in dental research. The congress is also open to non-members, who are kindly invited. Furter details of the Congress Programme will be made available as soon as possible.

Dr. Arvid Syrrist, Tandläkarhögskolan, Malmö, Sweden, is the General Secretary of the Congress.

International Journal of Health Education,

official organ of the International Union for Health Education of the Public. This is the *first international* health education periodical to be published. Printed in English and French editions quartely, its aim is to facilitate the exchange of experiences, ideas and news concerning health education and to bring to health workers and health education specialists throughout the world practical information which they can utilize in their work. It covers the following sections: health education in practice; professional training in health education; studies and research; methodology; international achievements; and national reports.

Price of the subscription is twelve (12.–) Swiss Francs per year. Requests for information should be addressed to the Editor, Miss Annette Le Meitour, 3, rue Viollier, Geneva, Switzerland.

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Aus der Hautklinik (Direktor: Prof. Sven Hellerström) des Karolinska Sjukhuset, Stockholm 60, Schweden

Ausgedehnte Moniliasis bei zwei Brüdern im Zusammenhang mit Antibioticabehandlung

von H. GENTELE und A. LODIN

Während der letzten zehn Jahre sind zahlreiche Arbeiten über örtliche und generalisierte Moniliasis erschienen. Viele Autoren, z. B. Waisman (11), McGivney (5), Stenderup und Mitarbeiter (10) u. a. sind der Ansicht, dass die in dieser Zeit klinisch eingeführten Antibiotica haben zur Zunahme dieser Pilzinfektionen beigetragen. Man findet auch ganz allgemein, selbst in bakteriologischen Lehrbüchern, die Angabe, dass *Candida albicans* oft als unschädlicher Saprophyt auf der Haut, im Magen-Darmkanal, in der Mundhöhle und Scheide vorkommt.

Zimmerman (14), Harris (2), Brown und Mitarbeiter (1) sowie andere vermuten, dass die klinischen Manifestationen der Moniliasis, welche als Komplikationen einer Behandlung mit Antibiotica auftreten können, auf einer Änderung der normalen Bakterienflora des Organismus beruhen. Hierbei soll es zu einem Ausfall des hemmenden Effekts dieser Mikroorganismen kommen, welche mit der gleichzeitig anwesenden *C. albicans* um Nährstoffe konkurrieren. Dass Veränderungen der Vitaminbiosynthese bei der Herabsetzung der Widerstandsfähighkeit gegenüber *C. albicans* Bedeutung besitzen können, nehmen u. a. Leitner (4) und Harris (2) an. Sie haben bei der Behandlung von Moniliasisinfektionen dadurch gute Erfolge erzielt, dass gleichzeitig mit den Antibiotica der Vitamin-B-Komplex gegeben wurde.

Nach Ansicht von Woods und Mitarbeitern (13) soll eine Unterdrückung Gram-negativer und Gram-positiver Bakterien durch Antibiotica *C. albicans* freieres Wachstum gewähren. Kligman (3) meint, Breitband-Antibiotica seien nicht imstande, Mund oder Darmkanal keimfrei zu machen, wohl aber halten sie empfindliche Mikroben im Schach, und hierauf folge ein gradweises Wiederwachsen antibioticaresistenter Keime, welche eine Zeitlang die ursprüngliche Flora ersetzen. Zimmerman (14) stellt die Theorie auf, dass ein beitragender Faktor in dem Verlust von für *C. albicans* wachstumshemmenden Substanzen liegen kann, welche normalerweise von der gewöhnlichen

Abb. 1–3. Moniliasis im Gesicht, an den Lippen, der Wangenschleimhaut und Zunge.

Darmflora produziert würden aber infolge der Vernichtung dieser Bakterien durch Antibiotica abwesend wären.

Wie der stimulierende Effekt der einzelnen Antibiotica sich auf das Wachstum von *C. albicans* in vivo und in vitro auswirkt, darüber gehen die Ansichten auseinander. Zimmerman (14) glaubt, dass diese Mittel das Pilzwachstum direkt steigern. Dieser Auffassung schliesst sich Moore (7) an, der fand, dass schwache Lösungen von Chlortetracyclin einen Reiz auf *C. albicans* ausübten, d.h. deutlich gesteigertes Wachstum im Vergleich zu Kontrollen. Seligman (9) hat bei seinen Tierversuchen nachgewiesen, dass eine subletale Dosis von *C. albicans* letal wird, wenn man sie mit Chlortetracyclin mischt. Auf Grund ihrer Untersuchungen in vitro sind dagegen Woods und Mitarbeiter (13) davon überzeugt, dass die Mittel das Pilzwachstum nicht fördern. Robinson (8) behauptet, weder Penicillin noch Breitband-Antibiotica leisten Moniliainfektionen Vorschub, sondern diese beruhen auf aus anderen Gründen herabgesetster Widerstandsfähigkeit gegenüber *C. albicans*. Im übrigen wird auf Arbeiten von beispielsweise Metzger und Mitarbeitern (7) sowie Wegmann (12) verwiesen, in welchen die Frage eingehend erörtert wird.

Welche Rolle die Einführung der Antibioticabehandlung hinsichtlich der grösseren Häufigkeit von Moniliainfektionen spielt, das darf wohl noch nicht als endgültig geklärt gelten. Vermutlich kommt hierbei auch anderen Faktoren Bedeutung zu. Im Hinblick auf das allgemeine Interesse des Problems erschien uns daher eine Veröffentlichung der folgenden Fälle gerechtfertigt.

Krankengeschichten

Fall 1. R. U. E., Knabe, 11 J.

Heredität. Bruder (Fall 2) hat dieselbe Affektion, sonst keine Hautkrankheiten in der Familie bekannt.

Frühere Erkrankungen. Von Kinderkrankheiten nur Schlarlach und Masern. Entfernung von adenoiden Vegetationen im Alter von 2 Jahren.

Jetzige Erkrankung. Im Alter von 1 Jahr erstmaliges Auftreten von rezidivierenden Mundwinkelrhagaden, umgeben von Erosionen mit geringen Belägen. Nach Penicillinbehandlung im Alter von 5 Jahren bei Masern akute Verschlimmerung, ähnliche Veränderungen nun auch hinter den Ohren, in der Umgebung der Augen, in Nasenlöchern, Mund und am Anus. Zustand wechselnd, Pat. doch nie ganz erscheinungsfrei. Wiederholt stationär behandelt. Seit 1951 auch lästige Conjunctivitis und Keratitis mit mehreren Rückfällen. 1953 Aufnahme in die Hautklinik zwecks eingehender Untersuchung.

Allgemeinbefund (1953). Blasser, magerer Knabe mit herabgesetztem Turgor. Innere Organe o.B.

Örtlicher Befund. Haut rings um die Augen gerötet und trocken mit scharfer, leicht schuppender Begrenzung. Augenlider geschwollen, eingetrocknetes Sekret zwischen den Wimpern. Mässige Rötung der Bindehaut auf beiden Seiten. An Nasenlöchern, Unterlippe, Mundwinkeln und Anus Rhagaden und starke Schuppung. Veränderungen in den Mundwinkeln vom Typ Perlèche. Auf der Zunge, in den Mundwinkeln, zum Teil auf der Wangenschleimhaut sowie am harten und weichen Gaumen stellenweise grauweisse Beläge, welche sich ziemlich leicht abheben lassen, wobei eine rote, feuchte Wundfläche zum Vorschein kommt (Abb. 1–3).

Untersuchungen. Übliche Blut- und Urinuntersuchungen o.B. S.R. 40–6 mm. Wa.R. negativ. — Ausstriche und Kulturen von Mundschleimhautherden und Faeces: *Monilia albicans.* — Komplementbindungsreaktion positiv für *Monilia* (Titer 1/40). — Trichophytinreaktion 1/50 positiv. — Röntgen, Lungen und Nasennebenhöhlen, o.B. — Porphyrine im Harn negativ. Lichttest negativ.

Verlauf und Behandlung. Das Krankheitsbild wurde zuerst in der Kinderklinik als Stevens-Johnsonsches Syndrom gedeutet. Ein ganzes Arsenal vershiedener Heilmittel hatte keinen merkbaren Einfluss: Chloromycetin, Aureomycin, Penicillin, Pyribenzamin, BAL, Vitamine B, Biotin, Lergigan, ACTH, Cortison u.a.m.

In der Hautklinik Behandlung mit Pinslungen und Mundspülungen mit 1 proz. Gentianaviolettlösung, ausserdem örtlich 1 proz. Rivanolvaseline; guter Erfolg. Eine Racheninfektion durch betahämolytische Streptokokken wurde mit Penicillin, ein späteres Rezidive derselben mit Aureomycin behandelt, beide Male ohne Verschlimmerung. Seit Entlassung 1953 erscheinungsfrei, 1957 jedoch kurzdauerndes Rezidive in der Umgebung der Nase.

Fall 2. L. E. E., Knabe, 8 J.

Heredität. S. Fall 1.

Frühere Erkrankungen. Nichts von Belang.

Jetzige Erkrankung. Nach Penicillinbehandlung im Alter von 2 Jahren bei Masern erstmaliges Auftreten von rezidivierenden Rhagaden und Schuppung hinter den Ohren, in der Umgebung der Augen, an Mundwinkeln und Anus. Zustand erheblich wechselnd, aber Pat. nie ganz erscheinungsfrei. Mehrere Male stationär behandelt.

Allgemeinbefund (1955). Blasser, magerer Knabe mit herabgesetztem Turgor. Innere Organe o.B.

Örtlicher Befund. An den Mundwinkeln, an der Oberlippe sowie rings um die Augen ist die Haut trocken und verdickt; hier und da Rhagaden. Zwischen den Wimpern eingetrocknetes Sekret, beträchtliche Rötung der Bindehaut beider Augen. Auf der Zunge, an den Mundwinkeln, Wangeschleimhaut, weichem und hartem Gaumen

Abb. 4–5. Moniliasisveränderungen.

stellenweise grauweisse Beläge, welche sich verhältnissmässig leicht entfernen lassen, wobei eine rote, feuchte wundfläche blossgelegt wird (Abb. 4–5).

Untersuchungen. Bluteosinophilie 2,5–11,5%, übliche Blut- und Urinuntersuchungen sonst o.B. S.R. 67–11 mm. Wa.R. negativ. — Ausstriche und Kulturen von Mundschleimhautveränderungen und Faeces: *Monilia albicans.* — Komplementbindungsreaktion positiv für *Monilia* (Titer 1/40–1/160). — Intracutanprobe mit *Monilia albicans* positiv nach 15 Min., desgl. nach 24 St. — Trichophytinreaktion 1/30 negativ. — Wiederholte Röntgenuntersuchungen der Lungen und Nasennebenhöhlen o.B. — Porphyrine im Harn negativ. Lichttest negativ. — Elektrophorese o.B. (bei einer Gelegenheit Gammaglobulin 21,9%). — Vidal negativ. — Antistreptolysin- und Antistaphylolysintiter widerholt normal.

Histopathologische Untersuchung. (Abb. 6). Hyperplastisches Epithel mit inter- und intrazellulärem Ödem sowie zahlreichen durchwandernden Leukocyten. Unter dem Epithel Zellinfiltration, aus Leukocyten, Lymphocyten und Plasmazellen bestehend. Pilze im Schnitt nicht mit Sicherheit nachweisbar; Mykose trotzdem gut denkbar.

Verlauf und Behandlung. Anfangs, als man der Ansicht war, es handle sich um Stevens-Johnsonsches Syndrom, machte man Versuche mit einer Menge von verschiedenen Heilmitteln, wie Penicillin, Chloromycetin, Aureomycin, Pyribenzamin, BAL, Vitamin-B-Komplex, Biotin, ACTH u.a.m. In der Hautklinik Behandlung hauptsächlich mit Pinslungen und Mundspülungen mit 1 proz. Gentianaviolettlösung; gutes Ergebnis. Nach der Entlassung jedoch leicht Rückfälle trotz weiterer örtlicher Behandlung. Im letzten Jahr indessen im grossen und ganzen beschwerdefrei.

Diskussion

Beiden Fällen gemeinsam ist Exazerbation bzw. erstmaliges Auftreten von Moniliasiserscheinungen im Anschluss an Penicillinbehandlung. Man kann sich schwer des Gedankens erwehren, dass dies das auslösende Agens war. Immerhin ist beachtenswert, dass beide Patienten später mit sowohl Penicillin wie Breitband-Antibiotica behandelt wurden, ohne dass sich die Pilzveränderungen verschlimmerten; allerdings waren sie bei diesen späteren Gelegenheiten gleichzeitig örtlich behandelt worden, was eine Exazerbation verhindert haben kann.

Abb. 6. Moniliasis. Die Mikrophotographie zeigt hyperplastisches Epithel, inter- und intrazelluläres Ödem sowie subepitheliale Zellinfiltration.

In beiden Fällen bestanden so grosse diagnostische Schwierigkeiten, dass beide in der Universitäts-Kinderklinik als Stevens-Johnsonsches Syndrom gedeutet wurden. Hier sind Ausstrichpräparate zum Pilznachweis wertvoll, ebenso Kulturverfahren.

In diesen Fällen brachte die örtliche Behandlung mit 1 proz. wässriger Gentianaviolettlösung grossen Nutzen, und innere, gegen die Mykose gerichtete Behandlung erübrigte sich.

Zusammenfassung

Nach einer kurzen Übersicht über das Schrifttum hinsichtlich der Rolle, welche die Antibiotica bei der Genese der Moniliasis spielen, wird über eine ausgedehnte Moniliainfektion im Anschluss an Antibioticabehandlung bei zwei Brüdern berichtet, mit erstmaligem Auftreten im Alter von 5 bzw. 2 Jahren.

Extensive moniliasis in two siblings in connection with antibiotic treatment.

A short review of what is known about the part played by antibiotics in the development of moniliasis. Report of two cases of extensive moniliasis infection in connection with antibiotic treatment in siblings aged 5 and 2 years respectively.

Moniliase étendue chez deux frères par rapport à un traitement avec des antibiotiques.

Après un résumé sur la littérature en ce qui concerne le rôle que jouent les antibiotiques dans la genèse d'une moniliase, on rapporte une infection étendue de moniliase se produisant à la suite d'un traitement avec des antibiotiques chez deux frères, chez qui les premiers symptômes se sont présentés à l'âge de 5 ans, respectivement 2 ans.

Extensa moniliasis en dos hermanos en relación con el tratamiento con antibióticos.

Después de una breve revisión bibliográfica con respecto al papel desempeñado por los antibióticos en la génesis de la moniliasis, se relata una extensa infección moniliásica en relación con el tratamiento con antibióticos en dos hermanos, aparecida primariamente a la edad de 5 y 2 años respectivamente.

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The Gaseous Metabolism of the New-born Infant Breathing 15% Oxygen

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Paul Bert (1870) is usually credited with the first demonstration that the new-born animal survives in nitrogen for much longer periods than the adult, but two centuries earlier Robert Boyle (1670) showed that the new-born kitten would survive about three times as long in a vacuum as an adult animal of the same size. Boyle observed that "these trials may deserve to be prosecuted with further ones to be made not only with such kittens, but with other very young animals of different kinds." This type of observation has been extended particularly by Himwich and his colleagues (1953).

It seems fairly obvious that this capacity to weather anoxia is shared by the new-born baby, but the evidence is necessarily more anecdotal and less controlled than in animals.

In the human adult the main defence against hypoxia is hyperventilation. By this means the partial pressure of oxygen in the alveolar air is raised nearer and nearer to the partial pressure of oxygen in the atmosphere which is being breathed. This hyperventilation can be maintained for indefinite periods when, say, 15% oxygen or less is being breathed.

In contrast, the infant, although appearing to have an active chemoceptor reflex (Cross & Warner, 1951; Cross & Oppe, 1953) hyperventilates for only a short period when first subjected to 15% oxygen, probably because of a central anoxic depression of the medulla. Presumably the response to still lower oxygen concentrations is of a similar pattern, but evidence of this should not perhaps be sought in the new-born baby.

It has been suggested by Himwich and his group of workers that anaerobic metabolism is the main method of maintaining energy production in the anoxic new-born. It should be noted that anaerobic glycolysis will give only about 7% (Krebs & Kornberg, 1957) of the energy obtained by the oxydative breakdown of glucose, and it is thus a most uneconomical method in an infant, whose supplies of glucose at birth are necessarily very limited. We proposed to investigate this matter in the new-born baby by using the

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changing CO_2 excretion in the expired air when breathing 15% O_2 as an index of anaerobic metabolism. Lactic acid is produced by the anaerobic breakdown of glucose and will displace CO_2 from the bicarbonate in the extra-cellular fluid; thus the additional CO_2 produced will be a measure of lactic acid production, which is in itself a measure of the energy being derived from the anaerobic breakdown of glucose. The disadvantage of this approach is that CO_2 excretion may not instantaneously reflect lactic acid production. The advantage, however, is that the infants may be examined while they are truly at rest, a state difficult to achieve with frequent blood sampling. Some of the results have been reported in summary form (Cross *et al.*, 1955).

Methods and Materials

The minute volume of respiration was measured in the body plethysmograph (Cross, 1949) and the expired gases were collected as previously described by the authors (for details see Cross and colleagues, 1957). The full term infants were examined in the Maternity Departments at St. Mary's Hospital, Paddington, and the Paddington General Hospital. Premature infants were examined in the Premature Baby Unit at Hammersmith Hospital. All examinations were carried out with the mothers' permission. After the infant had been at rest in the plethysmograph for twenty minutes a collection of diluted expired air was made for a period which varied between four to eight, and averaged 6.5 minutes. After an interval of approximately four minutes, and provided that the infant remained asleep, a second collection of expired air was made. When 15% oxygen was to be given it was supplied from a large meteorological gas balloon which had been filled from a high pressure cylinder through a humidifying bottle. From this balloon it was sucked over the infant's face. Four different types of experiment were performed.

(1) Eleven full term infants were examined on one occasion each, when two successive collections of diluted expired air were made while the infants were breathing air. This group acted as a control, and established the repeatability that could be expected if no other experimental procedure was undertaken. Results obtained from these infants are shown in Table 1.

(2) Sixteen examinations were made of fourteen full-term infants as follows: — A sample of gas was collected while the infant was breathing air and then 15% oxygen was supplied for an equilibration period of between four to nine minutes (average 4.5 minutes). The second collection of diluted expired air was then made while 15% oxygen was still being breathed. Results for these experiments are given in Table 2.

(3) Sixteen examinations were made of eleven premature infants, the procedure being the same as in Group 2, and the results are shown in Table 3.

(4) A further group of eight full-term infants was examined on ten occasions. This group was given 15% oxygen to breathe for at least five minutes before the first collection of expired gas was made. A second collection of expired gas was made after a short period of one to four minutes. The results from these infants are shown in Table 4.

TABLE 1

Full term babies on air (Period 1) followed by air (Period 2).

Subjects's No.	Age in days	Sex	Weight in kilos: At birth	Weight in kilos: At examination	Duration of test period, min.: Period 1	Duration of test period, min.: Between periods	Duration of test period, min.: Period 2	Average min. volume B.T.P.S.: Period 1, ml	Average min. volume B.T.P.S.: Period 2, ml	Average min. volume B.T.P.S.: % change of 2 on 1	Expired air: % O_2 Period 1	Expired air: % O_2 Period 2	Expired air: % CO_2 Period 1	Expired air: % CO_2 Period 2	Respiratory quotient: Period 1	Respiratory quotient: Period 2	Respiratory quotient: % change of 2 on 1	Oxygen consumed/kg/hour: Period 1, ml at N.T.P.	Oxygen consumed/kg/hour: Period 2, ml at N.T.P.	Oxygen consumed/kg/hour: % change of 2 on 1	Carbon dioxide produced/kg/hour: Period 1, ml at N.T.P.	Carbon dioxide produced/kg/hour: Period 2, ml at N.T.P.	Carbon dioxide produced/kg/hour: % change of 2 on 1
43	8.93	F	2.86	2.81	7	1	7	417	438	+ 5.0	15.18	15.00	5.01	4.96	.84	.80	− 4.8	441	481	+ 9.1	369	383	+ 3.8
44	2.92	M	3.77	3.52	7	1	7	354	303	− 14.4	13.62	13.00	5.59	6.10	.72	.72	0	382	355	− 7.1	274	256	− 6.6
45	9.90	M	3.29	3.18	8	1	7	483	480	− 0.6	14.94	15.04	5.08	5.03	.81	.82	+ 1.2	460	449	− 2.4	373	367	− 1.6
46	3.94	M	3.40	3.26	8	1	8	328	383	+ 16.8	14.38	15.03	5.33	4.69	.77	.75	− 2.6	336	355	+ 5.7	259	266	+ 2.7
47	6.71	M	3.63	3.40	8	2	8	365	381	+ 4.4	13.14	13.85	6.16	5.46	.74	.72	− 2.7	434	414	− 4.6	323	299	− 7.4
48	6.56	F	3.18	3.09	7	3	7	420	384	− 8.6	15.36	14.40	4.99	5.83	.87	.86	− 1.1	383	411	+ 7.3	332	355	− 6.9
49	5.34	F	3.20	2.98	7	5	7	348	411	+ 18.1	14.41	14.63	5.17	5.02	.75	.75	0	397	453	+ 11.4	297	341	+ 11.5
50	3.71	M	2.72	2.55	7	5	7	432	363	− 16.0	15.60	14.52	4.43	5.34	.79	.79	0	469	471	+ 0.4	369	373	+ 1.1
51	3.48	M	3.57	3.37	7	5	7	345	344	− 0.3	13.54	14.18	5.54	5.02	.70	.69	− 1.4	394	360	− 8.6	276	249	− 9.8
52	2.14	F	3.20	3.12	7	2.6	7	381	324	− 15.0	15.06	14.09	4.72	5.68	.76	.79	+ 3.9	377	370	− 1.9	286	292	+ 2.1
53	0.14	F	3.23	3.23	7	5	7	537	468	− 12.8	15.81	15.64	4.28	4.38	.79	.79	0	437	394	− 9.8	347	310	− 10.7
Mean	4.89		3.28	3.14	7.27	2.9	7.18	401	389	− 2.13	14.64	14.49	5.12	5.23	.78	.77	− 0.07	410	410	− 0.045	319	317	− 0.73
S.D/σ	2.93		0.31	0.28				64.8	56.4	12.4	0.89	0.71	0.54	0.51	0.05	0.05	2.28	40.9	47.5	7.41	42.3	48.9	7.16

TABLE 2

Full term babies on air (Period 1) followed by 15% oxygen (Period 2).

Subject's No.	Age in days	Sex	Weight in kilos: At birth	Weight in kilos: At examination	Duration of test period, min.: Period 1, breathing air	Duration of test period, min.: Between periods breathing 15% O_2	Duration of test period, min.: Period 2, breathing 15% O_2	Average min. volume B.T.P.S.: Period 1, ml	Average min. volume B.T.P.S.: Period 2, ml	Average min. volume B.T.P.S.: % change of 2 on 1	Expired air: % O_2 Period 1	Expired air: % O_2 Period 2	Expired air: % CO_2 Period 1	Expired air: % CO_2 Period 2	Respiratory quotient: Period 1	Respiratory quotient: Period 2	Respiratory quotient: % change of 2 on 1	Oxygen consumed/kg/hour: Period 1, ml at N.T.P.	Oxygen consumed/kg/hour: Period 2, ml at N.T.P.	Oxygen consumed/kg/hour: % change of 2 on 1	Carbon dioxide produced/kg/hour: Period 1, ml at N.T.P.	Carbon dioxide produced/kg/hour: Period 2, ml at N.T.P.	Carbon dioxide produced/kg/hour: % change of 2 on 1
54	1.27	F	2.95	2.81	6	5	7	333	252	−24.3	14.16	6.93	4.92	5.80	.67	.73	+ 9.0	426	352	−17.4	286	257	−10.1
55	3.93	F	2.95	2.75	6	4	8	333	386	+15.9	14.04	10.08	6.07	4.50	.85	.90	+ 5.9	426	346	−18.8	362	312	−13.8
56	5.66	F	3.23	2.81	7	4	8	311	244	−21.6	12.58	5.84	5.83	6.83	.64	.72	+12.5	488	401	−17.8	314	290	− 7.7
57	2.08	M	2.81	2.55	7	4	7	573	490	−14.5	16.26	10.18	3.31	3.53	.65	.72	+10.8	558	466	−16.5	364	335	− 8.0
57	9.08	M	2.81	2.75	7	5	8	565	577	+ 2.1	15.89	10.59	4.65	4.82	.90	1.10	+22.2	525	460	−12.4	471	501	+ 6.4
58	8.96	M	3.46	3.37	6	4	6.5	497	558	+12.5	15.25	10.84	4.74	3.90	.79	.95	+20.3	438	339	−22.6	347	322	− 7.2
59	5.33	M	2.95	2.69	6	9	7	329	388	+17.9	14.89	10.51	5.15	4.10	.82	.88	+ 7.3	379	330	−12.9	310	291	− 6.1
60	4.21	F	3.06	2.95	7	4	6	549	580	+ 5.6	16.30	10.62	3.55	3.70	.72	.79	+ 9.7	452	428	− 5.3	324	340	+ 4.9
60	8.22	F	3.06	2.98	6	4	7	500	508	+ 1.6	14.74	10.26	4.89	4.29	.74	.86	+16.2	554	426	−23.1	412	369	−10.4
61	6.02	F	3.18	3.15	6	4	7	497	505	+ 1.6	13.76	9.20	5.76	5.19	.76	.84	+10.5	598	497	−16.9	453	417	− 8.0
62	4.00	M	4.45	4.17	6	4	7	518	456	−12.1	13.62	8.34	5.53	5.22	.71	.74	+ 4.2	469	372	−20.7	331	277	−16.3
63	5.75	F	3.46	3.26	6	4	4	364	394	+ 8.2	13.54	8.90	5.83	5.41	.74	.86	+16.2	407	356	−12.5	303	306	+ 1.0
64	6.87	M	3.63	3.29	5	4	5	365	416	+13.8	12.53	9.44	7.35	5.39	.84	.93	+10.7	470	357	−24.0	397	332	−16.4
65	8.33	F	3.01	3.20	6	4	6	434	455	+ 4.8	14.41	10.13	5.30	4.38	.77	.86	+11.7	465	360	−22.6	356	310	−12.9
66	4.08	F	4.08	3.77	6	5	7	525	554	+ 5.6	15.81	10.96	3.83	3.26	.70	.79	+12.9	380	305	−19.7	265	240	− 9.4
67	11.05	M	3.35	3.18	7	4	7	383	459	+19.9	14.62	9.97	5.38	4.87	.82	.96	+17.1	389	361	− 7.2	318	347	+ 9.1
Mean	5.93		3.28	3.11	6.25	4.5	6.72	442	451	+ 2.3	14.53	9.55	5.13	4.70	.76	.85	+12.3	464	385	−16.9	351	328	− 6.6
SD	2.69		0.46	0.42				94.9	102.5	13.7	1.18	1.44	1.01	0.93	.075	.104	4.99	66.4	55.2	5.57	57.8	62.9	7.86

TABLE 3

Premature babies on air (Period 1) followed by 15 % oxygen (Period 2).

Subject's No.	Age in days	Sex	Weight in kilos: At birth	Weight in kilos: At examination	Duration of test period, min.: Period 1, breathing air	Duration of test period, min.: Between periods breathing 15 % O_2	Duration of test period, min.: Period 2, breathing 15 % O_2	Average min. volume B.T.P.S.: Period 1, ml	Average min. volume B.T.P.S.: Period 2, ml	Average min. volume B.T.P.S.: % change of 2 on 1	Expired air: % O_2 Period 1	Expired air: % O_2 Period 2	Expired air: % CO_2 Period 1	Expired air: % CO_2 Period 2	Respiratory quotient: Period 1	Respiratory quotient: Period 2	Respiratory quotient: % change of 2 on 1	Oxygen consumed/kg/hour: Period 1, ml at N.T.P.	Oxygen consumed/kg/hour: Period 2, ml at N.T.P.	Oxygen consumed/kg/hour: % change of 2 on 1	Carbon dioxide produced/kg/hour: Period 1, ml at N.T.P.	Carbon dioxide produced/kg/hour: Period 2, ml at N.T.P.	Carbon dioxide produced/kg/hour: % change of 2 on 1
1	1.19	F	2.19	2.04	5	6	5	335	365	+ 9.0	16.80	11.25	3.10	2.81	.70	.69	− 1.4	352	360	+ 2.3	248	247	− 0.4
2	1.63	F	2.04	1.96	6	4	6	367	327	−10.9	16.71	10.51	2.99	3.13	.65	.65	0	421	395	− 6.2	274	258	− 5.8
2	2.65	F	2.04	2.04	6	4	6	325	351	+ 8.0	15.79	10.61	3.63	3.26	.65	.68	+ 4.6	431	400	− 7.2	280	274	− 2.0
3	5.58	M	1.93	1.79	6	4	6	251	282	+12.4	16.07	11.17	3.69	3.31	.71	.78	+ 9.9	361	330	− 8.6	255	259	+ 1.6
5	2.83	M	1.70	1.61	7	4	7	375	351	− 6.4	17.60	12.87	2.21	1.97	.60	.62	+ 3.3	409	337	−17.6	246	208	−15.4
6	12.31	F	1.81	1.64	5	4	7	399	372	− 6.8	16.08	10.63	3.97	4.14	.78	.87	+11.5	606	528	−12.9	470	459	− 2.3
8	11.69	M	1.33	1.47	6	5	7	322	270	−16.1	15.97	9.88	4.54	5.23	.89	.97	+ 9.0	552	488	−11.6	490	476	− 2.9
9	2.79	F	2.14	2.06	6	5	6	263	264	+ 0.4	14.51	8.72	4.72	4.66	.68	.69	+ 1.5	433	428	− 1.2	295	294	− 0.3
10	5.27	M	1.86	1.81	6	4	7	336	342	+ 1.8	17.11	11.77	3.39	3.23	.85	.92	+ 8.2	367	334	− 9.0	314	306	− 2.5
10	7.29	M	1.86	1.83	6	5	6	374	361	− 3.5	16.84	10.95	3.58	3.99	.84	.93	+10.7	438	426	− 2.7	367	397	+ 8.2
10	12.33	M	1.86	1.93	6	4	8	334	365	+ 9.3	16.19	11.36	3.66	3.31	.72	.82	+13.9	410	378	− 7.8	296	309	+ 4.4
11	10.13	M	2.10	2.00	6	4	6	427	392	− 8.2	16.58	10.82	4.04	4.05	.90	.96	+ 6.7	478	419	−12.3	432	400	− 8.0
12	4.01	F	2.02	1.87	6	4	4.5	277	299	+10.7	15.83	10.48	3.86	3.83	.705	.76	+ 7.8	406	379	− 6.7	286	287	+ 0.3
12	13.0	F	2.02	1.97	6	4	6	413	350	−15.3	17.22	11.59	3.47	3.80	.91	1.02	+12.1	388	323	−16.8	353	331	− 6.2
13	7.04	M	1.86	1.81	6	5	7	343	333	− 2.9	16.39	10.96	4.03	3.80	.85	.93	+ 9.4	441	373	− 7.7	377	348	− 7.7
13	9.10	M	1.86	1.91	6	5	7	280	264	− 5.7	16.46	10.64	4.31	4.41	.95	1.04	+ 9.5	330	293	−11.2	312	304	− 2.6
Mean	6.80		1.91	1.86	5.9	4.4	6.3	339	331	− 1.5	16.38	10.89	3.70	3.68	0.77	0.83	+ 7.3	426	387	− 8.6	331	322	− 2.6
SD	4.15		0,20	0.17				52.6	41.7	9.55	0.72	0.89	0.62	0.78	0.11	0.14	4.49	71.3	61.7	5.28	77.3	76.0	5.44

TABLE 4

Full term babies on 15 % oxygen (Period 1) followed by 15 % oxygen (Period 2).

Subject's No.	Age in days	Sex	Weight in kilos: At birth	Weight in kilos: At examination	Duration of test period, min.: Period 1	Duration of test period, min.: Between periods	Duration of test period, min.: Period 2	Average min. volume B.T.P.S.: Period 1, ml	Average min. volume B.T.P.S.: Period 2, ml	Average min. volume B.T.P.S.: % change of 2 on 1	Expired air: % O_2 Period 1	Expired air: % O_2 Period 2	Expired air: % CO_3 Period 1	Expired air: % CO_3 Period 2	Respiratory quotient: Period 1	Respiratory quotient: Period 2	Respiratory quotient: % change of 2 on 1	Oxygen consumed/kg/hour: Period 1, ml at N.T.P.	Oxygen consumed/kg/hour: Period 2, ml at N.T.P.	Oxygen consumed/kg/hour: % change of 2 on 1	Carbon dioxide produced/kg/hour: Period 1, ml at N.T.P.	Carbon dioxide produced/kg/hour: Period 2, ml at N.T.P.	Carbon dioxide produced/kg/hour: % change of 2 on 1
68	0.89	M	3.15	3.11	7	1	6	504	504	0	10.14	10.32	3.56	3.49	.70	.72	+2.9	403	388	− 3.7	284	278	− 2.1
68	1.75	M	3.15	3.02	7	1	6	399	389	−2.5	9.52	9.67	4.38	4.31	.78	.79	+1.3	370	350	− 5.4	288	276	− 4.2
69	4.13	F	3.77	3.74	7	1	6	600	588	−2.0	10.86	11.43	3.77	3.46	.93	.98	+5.4	326	276	− 15.3	302	271	− 10.3
69	5.99	F	3.77	3.80	7	1	6	480	493	+2.7	9.41	9.83	5.04	4.82	.90	.94	+4.4	352	332	− 5.7	318	312	− 1.9
70	0.94	M	3.32	3.26	6	1	6	382	368	−3.7	9.08	9.10	4.41	4.67	.72	.77	+6.9	357	340	− 4.8	256	261	+ 2.0
71	11.75	F	3.29	3.33	5	4	7¼	512	531	+3.7	9.64	10.21	4.96	4.77	.93	1.01	+8.6	412	377	− 8.5	382	381	− 0.3
72	5.54	F	3.77	3.54	6	1	6	394	375	−4.8	9.78	9.85	4.21	4.43	.77	.83	+7.8	304	283	− 6.9	233	234	+ 0.4
73	6.04	M	3.35	3.12	6	1	6	385	351	−8.8	9.53	9.09	4.86	5.28	.83	.84	+1.2	357	350	− 2.0	295	293	− 0.7
74	4.19	F	3.03	2.75	6	1	6	270	270	0	9.52	9.69	4.95	5.05	.84	.90	+7.1	285	274	− 3.9	240	246	+ 2.5
75	7.42	F	3.18	3.18	6	1	6	424	427	+0.7	10.05	10.12	4.80	5.09	.88	.96	+9.1	364	356	− 2.2	320	342	+ 6.9
Mean	4.86		3.38	3.29	6.3	1.3	6.13	435	430	−1.5	9.75	9.93	4.49	4.54	0.83	0.88	+5.47	353	333	− 5.84	292	289	− 0.77
SD	3.32		0.29	0.33				91.6	97.2	3.72	0.5	0.67	0.52	0.63	0.08	0.10	2.92	39.7	41.3	3.88	43.8	44.8	3.82

As soon as the collections of expired air had been completed Haldane analysis was made of the gases in the aspirator bottles and also of the 15% oxygen in the meteorological balloon.

The subject's numbers, which will be seen in the Tables opposite each individual baby, are chosen to be in series with those in the previous paper by the present authors in this journal. The results on the premature babies have already been reported as far as their performance while breathing air is concerned. Eleven of the fourteen studies of the original paper are repeated here, together with the results obtained when 15% oxygen was breathed.

Results

Clinical

Cyanosis was not apparent in all babies on 15% oxygen, and even if present was never severe. It was noted that following administration of 15% oxygen some of the babies felt flaccid and appeared sleepy on removal from the plethysmograph. On several occasions the nursing staff concluded erroneously that drugs had been given. As expected, no ill effects have been observed in any baby receiving 15% oxygen.

Minute volume

Fig. 1 shows the results from the four types of experiment. It will be observed that the average minute volume of respiration during the second period of examination, whether air or 15% oxygen was being breathed, did not differ significantly from the average of the first control period. If deductions are to be drawn from the results of the respiratory quotient, it is very important to establish first of all that the 15% oxygen did not cause hyperventilation. Hyperventilation by washing out CO_2 will of course raise the respiratory quotient in the absence of any change in metabolism.

Respiratory quotient

It will be seen from Fig. 1 that babies who breathed air on the two occasions showed no significant change of respiratory quotient. However, both premature and full term infants who breathed air first and 15% oxygen later showed a highly significant rise of R.Q. (12.3% for full term, 7.3% for prematures). Full term infants receiving 15% oxygen for a second period showed a slight, but significant, rise of R.Q. (+5.5%).

Oxygen consumption

It will be seen that the infants breathing 15% oxygen after air showed a significant fall of oxygen consumption, the extent of which—16.9% for full term and 8.6% for premature babies—was a complete surprise to us.

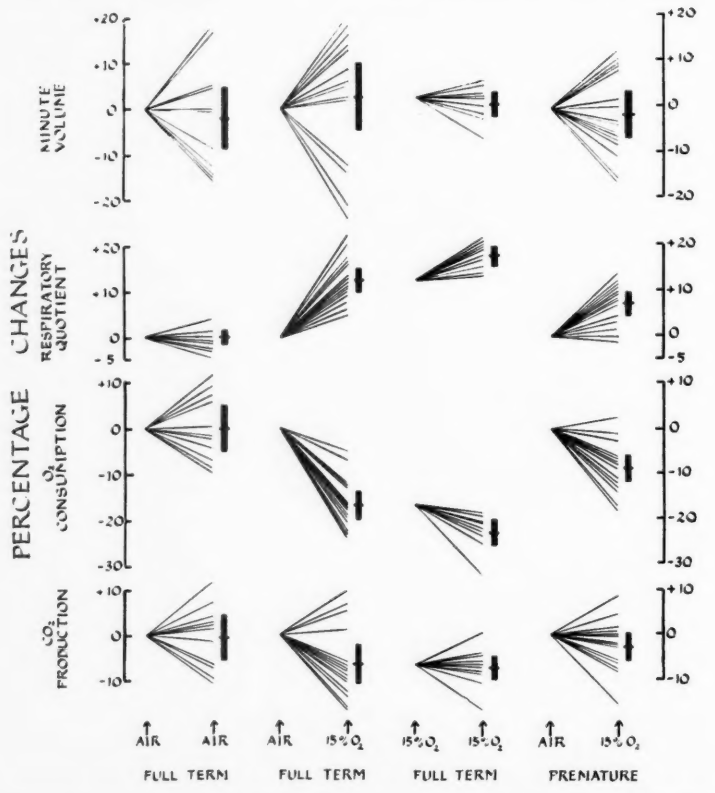

Fig. 1. Showing the percentage changes of CO_2 production, O_2 consumption, respiratory quotient and minute volume of respiration during Periods 1 and 2 for the four groups of infants examined. For each individual baby the value in Period 1 has been taken as 100% and the value in Period 2 has been expressed as a percentage of this. The thin sloping lines represent these pairs of results in any one baby. The thick vertical line, beside a group of observations, defines the 95% confidence limit of the mean of the observations in Period 2, and the horizontal line through it shows the arithmetic mean. For the full term babies, breathing 15% O_2 on both occasions, it has been assumed that the mean of their point of origin in Period 1 is the same as the mean at the end of Period 2 for the full term babies breathing 15% O_2 after breathing air. While this assumption is not strictly warranted (the point of origin will be 19 times out of 20 within the limit defined by the 95% confidence limit in the previous column) it has the advantage of presenting the collected data in one diagram.

In fact, of the 32 occasions on which premature or full term infants were examined on the low oxygen mixture after air, all but one showed a fall in oxygen consumption. This fall was highly significant for both groups. The infants receiving 15% oxygen on a second occasion showed a further fall in oxygen consumption (-5.8%).

Carbon dioxide production

The results for carbon dioxide production are less clear cut. There was no significant rise in CO_2 production on breathing 15% oxygen, and the full term infants showed a signficant fall (-6.6%).

Changes in relation to age

Of all the correlations examined only four significant relationships between the age of the infant and other values were found. These are illustrated in Fig. 2, together with one non-significant relationship for purposes of comparison.

Age and change in minute volume

It will be observed that for full term, but not premature, infants there is a significant relationship between their age and the percentage change of the minute volume while breathing 15% oxygen compared with the minute volume while breathing air. (As stated above, there was no significant change in the *mean* minute volume for the group as a whole.) In previous work, when we have given 15% oxygen to full term infants, this relationship between age and the minute volume of respiration had not been noted (Cross & Warner, 1951, Cross & Oppe, 1953). Such a relationship has, however, been reported by Miller (1955). But in spite of the hyperventilation shown by the infants of seven days and older, there was no significant relationship between change in R.Q. and change in minute volume (correlation coefficient between rise in R.Q. and change in minute volume is $+0.147$; $p > 0.8 < 0.9$).

Age and change in respiratory quotient

In Fig. 2 it is also shown that there is a positive correlation both for full term infants and premature infants between their age and the percentage change in respiratory quotient when 15% oxygen is breathed after breathing air ($P < 0.001$ for prematures: $p < 0.01$ for full term babies). The younger the infant the less does the respiratory quotient rise. If a rise in respiratory quotient may be regarded as an index of the onset of anaerobic metabolism, this finding is at variance with the view expressed by Himwich and others, that the anaerobic pathway is a good defence against anoxia and is most available at birth, declining afterwards. Superficial examination of our results would suggest that the youngest infants are least able to undertake anaerobic metabolism, but at least some of the rise of the respiratory quotient in the older infants should perhaps be attributed to the hyperventilation which was noted above. For comparison the results are given for the babies who breathed air during both experimental periods. It will be

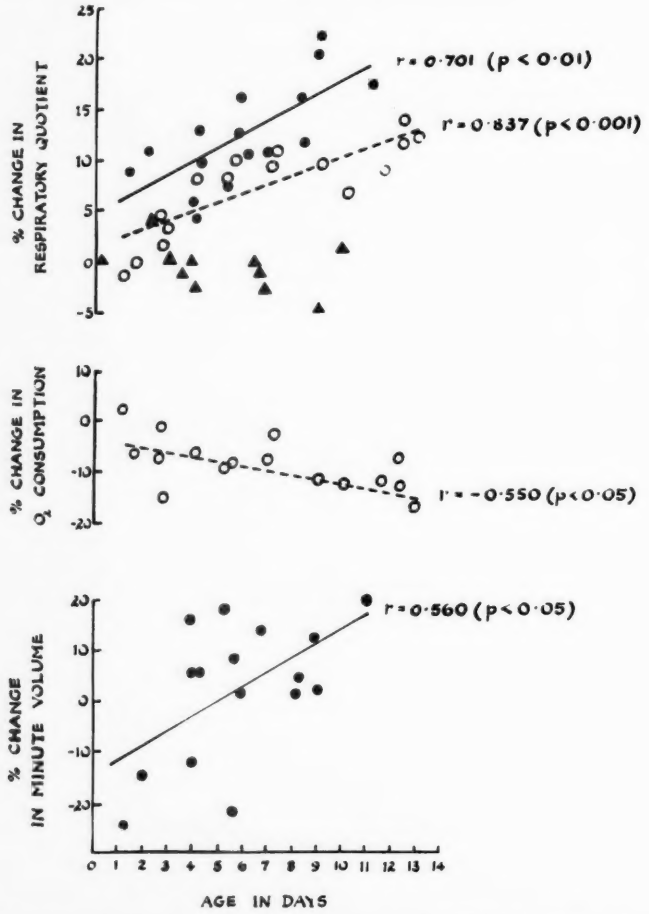
% CHANGE IN RESPIRATORY QUOTIENT
r = 0·701 (p < 0·01)
r = 0·837 (p < 0·001)
% CHANGE IN O2 CONSUMPTION
r = −0·550 (p < 0·05)
% CHANGE IN MINUTE VOLUME
r = 0·560 (p < 0·05)
AGE IN DAYS

Fig. 2. Data concerning percentage change in respiratory quotient, oxygen consumption and minute volume, all in relation to age of the subjects.

● ——— ● = full term infants breathing 15 % O_2 in Period 2 after air in Period 1 (Table 2).
O – – – O = premature infants similarly treated (Table 3).
▲ = full term infants receiving air on both occasions. These last infants show no consistent change of R.Q. (Table 1).

noted that there is no significant relationship in these infants, between the change in respiratory quotient and their age.

Age of premature babies and change in oxygen consumption

Lastly, in Fig. 2 there is shown a rather surprising relationship between the age of the premature infants and the percentage change of oxygen

consumption which was found when 15% oxygen was breathed after a period of breathing air. It will be noted that when breathing 15% oxygen, the oxygen consumption falls more in the premature babies nearer two weeks of age than in those in the first few days of life. No such relationship for oxygen consumption with age is found for the full term infants.

Discussion

Anaerobic Metabolism as Judged by Respiratory Quotient

In using the rise of respiratory quotient as an index of the fixed acid production by the infant, obviously very considerable assumptions are being made. One does not know, for example, how quickly the fixed acids diffuse from the cells and hence come into a situation where carbon dioxide can be displaced from the bicarbonate of extracellular fluid. The tacit assumption is made here that an equilibrium state is achieved, but this may well not be so, and it is probable that the rise in carbon dioxide production due to displacement from bicarbonate is, if anything, an understatement of fixed acid production. Also a rise in R.Q. as an index of increased lactic acid production is only valid if the alveolar ventilation remains constant. While we have no direct measure of alveolar ventilation, it seems reasonable to accept the lack of change of average minute volume on the low oxygen mixture as evidence for this. It has been stated above that while there is no significant change of average minute volume for the whole groups of full term and premature infants on breathing 15% oxygen after air, individual full term infants do show a significant relationship between their ages and changes in minute volume. Hyperventilation shown by the older full term infants must have some effects on the individual R.Q.'s, but, as shown above, this relationship is not demonstrable.

The greater increase in R.Q. in the baby around one week after birth compared with the newly born baby may, therefore, also suggest that anaerobic metabolism is more readily available for the older infant. This suggestion is supported by our findings in the premature infants in whom there is a rise in R.Q. with age without any corresponding rise in minute volume. This is an unexpected result, since animal experiments suggest that the ability to withstand anoxia decreases rapidly after birth (Fazekas, Alexander & Himwich, 1941).

As shown above, the R.Q.'s for the whole groups of full term and premature infants rise on a low oxygen mixture. However, when the components of this ratio are studied it will be seen that the total CO_2 production has fallen, instead of rising, although the fall has been less pronounced than that of the oxygen consumption. Since much less energy is produced (per g of

glucose) by anaerobic than by aerobic glycolysis, any anaerobic glycolysis will have far from compensated for the decline in aerobic metabolism. The calculation in Appendix I gives an estimate of the total energy deficit.

Both the possibly increased availability of anaerobic glycolysis for the older neonate and, much more significant, its failure to compensate for the fall in aerobic glycolysis, suggest that anaerobic metabolism does not provide an important defence against hypoxia in the earliest days of life.

It will be noted that no direct evidence has been brought forward here to show that lactic acid is in fact produced by the infant breathing 15% O_2. Satisfactory direct evidence could only be obtained by repeated arterial puncture, and we have not thought it justifiable to do this. If we suppose that there is no lactic acid production, and the consistent changes in R.Q. are entirely produced by relative increase of alveolar ventilation with diminution of dead space in anoxia, then it also follows that there is no attempt on the part of the infant to maintain metabolism, and that the fall in energy production is even greater than our estimate (Appendix I).

Aerobic Metabolism

The remarkable drop in oxygen consumption in the new-born infant shortly after exposure to mild hypoxia has already been noted. Since estimations were made over short periods of time we had to exclude the possibility that metabolism was being maintained on stored oxygen. When a baby first starts to breathe a low oxygen mixture, then all compartments of the body will come into equilibrium with a low partial pressure of oxygen. While this new equilibrium is being attained, measurement of oxygen removed from the inspired air (even if it were continuous) would not represent the rate at which oxygen was being metabolised by the cells, even if this latter rate were unaltered. An estimate of this store of oxygen has been made, and it appears that the volume involved is quite insufficient to compensate for the fall in oxygen consumption as measured.

In this series of babies we have incomplete data about the body temperature during the administration of the low oxygen mixture, which was taken on some occasions with a clinical thermometer immediately before and after completion of the test. As this sometimes showed a fall, further work on this has been undertaken by Brodie, Cross & Lomer (1957), and this shows that the rectal temperature as measured with a thermocouple over a period of administration of low oxygen for 50 minutes does not show any systematic change. It should therefore be emphasised in this present connection that the fall in oxygen consumption is not associated with evidence of fall in body temperature during the first 50 minutes of administra-

tion of low oxygen mixture. It would seem unlikely that the body temperature could be maintained indefinitely at its control level if energy production is truly reduced, and it is of great interest to note that Sjöstedt and Rooth (1957), who gave 15% O_2 to full term babies for a week for another purpose, found that their body temperatures were indeed lowered.

Anoxia in Adults

It has been stressed that we find that the new-born baby lowers his oxygen consumption when anoxic, but it is important to compare this situation with the reaction to anoxia in the adult. For this purpose we propose to confine ourselves to the adult human subject.

A comparison with other mammals will not be stressed here, although it should be noted that this matter has been admirably dealth with by Acheson, Dawes & Mott (1956), who studied the oxygen consumption in anoxic foetal and new-born lambs. Briefly, one may state that it is now established that anoxia, a fall in oxygen in the inspired air, causes a fall in oxygen consumption in new-born lambs, puppies and kittens. In contrast, the adults of these animals are all able, by overbreathing, to maintain their oxygen consumption at a constant level even in the face of quite severe anoxia.

Van Liere, in his excellent monograph on "Anoxia, its effect on the body" (1942) summarises the situation up to that date by stating that "it is now generally believed that gaseous metabolism is independent of variations in barometric pressures". He is referring to the maintenance of oxygen consumption by the adult at altitudes of up to 20,000 feet (i.e., equivalent of about 10% O_2 at sea level). If one accepts Paul Bert's classical experiments demonstrating that the physiological effects of low barometric pressure are due to the fall of the partial pressure of oxygen, and independent of the absolute barometric pressure, one may take this statement to apply to anoxia induced by the administration of a gas mixture low in oxygen content, but applied at atmospheric pressure. In a more recent work Lillienthal *et al.*, (1946) during experiments primarily concerned with the gradient of oxygen pressure between alveolar air and arterial blood, found incidentally that oxygen consumption of subjects at rest and breathing a mixture of oxygen and nitrogen (which was between 10–11% oxygen) fell, on an average, from 285 ml/min on air to 258 ml/min (−10%). However, these resting subjects were studied "at rest while lying supine or standing quietly". The tables in this paper do not state which of the two postures was assumed in individual readings, and for this reason it is not possible to make a valid comparison between resting on air and resting on the low oxygen mixture when a change of oxygen tension is the only variable. This seems important, as

Passmore & Durnin (1955) show that standing at ease will raise the calorie expenditure by 21% above lying at ease. It is also noteworthy in assessing the importance to be attached to the finding of Lilienthal *et al.*, which is discrepant from the majority of authors, that in the succeeding year one of the same workers (Houston & Riley, 1947) found that "values for CO_2 output, O_2 intake and R.Q. remained nearly constant during rest at all altitudes" (up to 22,000 ft). They quote three further recent papers in support of this finding, and mention only one discrepancy in the literature (Cook, 1945). It would appear, therefore, that Riley, who is an outstanding investigator in this field, does not accept the data of Lilienthal *et al.* (1946) in relation to the fall of oxygen consumption at lowered partial pressure of oxygen in the adult human subject. Cook (1945) was concerned with the specific physical effects of low barometric pressure. Human subjects were given pure oxygen to breathe at 18, 30 and 38 thousand feet (simulated). As he mentions, the partial pressure of pure oxygen at 36,000 feet is about 150 mm Hg, which is almost the same as that of air at ground level. Cook's findings therefore cannot be considered to be concerned with anoxia, if this term is considered to imply a lowered partial pressure of oxygen in the inspired air. More recently, Pugh (1957) failed to find any fall in oxygen consumption in one subject on Everest at 20,500 feet.

We feel that it is justifiable to claim that the baby made hypoxic by breathing 15% oxygen differs from the adult in the same situation in that the oxygen consumption of the baby falls while that of the adult is maintained. It is appreciated that as the new-born baby does not respond to anoxia by overbreathing, it is probable that the same level of oxygen in the inspired air will imply a more severe arterial anoxia in the baby than in the adult. We have no direct measurement of the alveolar gas tensions, but we have figures for the level of oxygen in the expired air of the babies. In the full term infants there are 36 estimates, 34 of which fell between 8.3 and 11.4 per cent, with a mean of 10 per cent. (Two markedly low values of 6.9 and 5.8 per cent were found (see Table 2) in babies, in whom the minute volume of respiration fell heavily.) The remaining figures give a pO_2 of 71 mm Hg in the expired air. If the difference existing between pO_2 in expired and alveolar air is, as in the adult, about 12 mm Hg, the mean alveolar pO_2 of our babies would be about 59 mm Hg. One must add to this the distinct possibility that the alveolar–arterial gradient is greater in the baby than in the adult. But the oxygen dissociation curve of the baby's blood will presumably be shifted to the left of the adult's curve (Dill) and even if the arterial pO_2 were as low as 50 mm Hg this would still represent an oxygen saturation in the arterial blood of 85 per cent or more.

Energy Production of Anoxic Baby

In Appendix I a calculation is set out which is an attempt to estimate the energy production of the new-born baby while breathing 15% O_2. It is calculated that the "average full term baby" has a fall in energy production of about 15% on the low oxygen mixture. On the group of full term infants who received the low oxygen mixture on two occasions (Table 4), one finds that on the second occasion there is a further fall in oxygen consumption of 5.8% ($p < 0.001$) without any significant rise in CO_2 production, so one may assume that the estimate made of a fall in energy production is low.

It would appear, therefore, that in the new-born baby there is not a basal rate of metabolism which will be maintained under all conditions. In this respect the baby does not conform to Claude Bernard's famous generalisation "la fixité du milieu intérieur est la condition de la vie libre indépendante". One is tempted to feel that Claude Bernard was right, and that in fact the baby may not be regarded as having a genuinely free and independent existence.

If the energy production of the anoxic baby falls, then either his temperature will in due course fall, or his heat loss will be greatly reduced. Both may well occur. In further work Brodie and his colleagues have shown, by a method of quasi-direct calorimetry, that there is indeed a fall in heat output during the administration of 15% O_2 for a period of 50 minutes (1957). Further, as already quoted, Rooth and his colleagues have shown that there is an actual fall in body temperature when 15% O_2 is given for a week.

Survival of Baby in Anoxia

It is impossible at the moment to answer with certainty the question "how does the baby survive anoxia?", but it seems tolerably certain that the findings presented here, that an immediate fall of oxygen consumption follows mild anoxia, must be taken into account when this matter is discussed. We have presented evidence that at this level of anoxia in the new-born baby the rate of metabolism is lowered, and not maintained by uneconomical methods such as anaerobic metabolism. It is, of course, quite possible that in certain parts of the body different reactions are occurring, and one of the most tantalising questions which we would like to answer is whether the oxygen consumption of all parts of the body falls equally under these conditions. There is no direct evidence on this matter, but the following three facts may provide a hint. Firstly, premature infants show a fall in oxygen consumption on low oxygen which is markedly and signific-

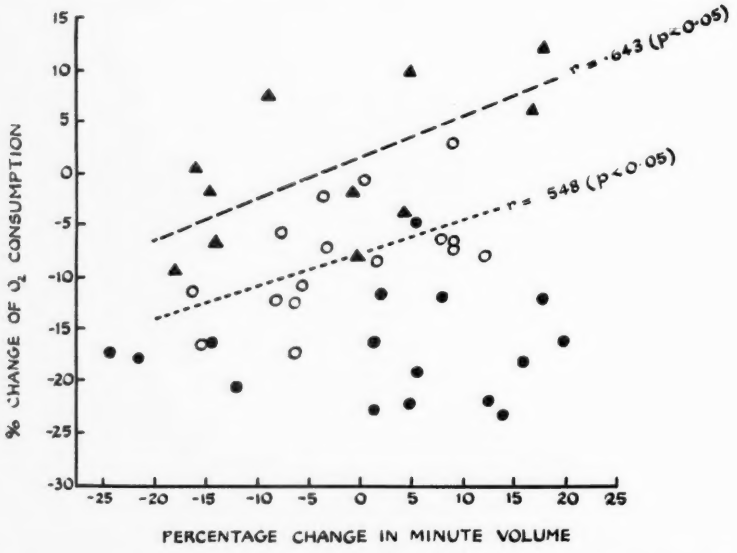

Fig. 3. Illustrating the relationship between percentage change of oxygen consumption and percentage change in minute volume. Each percentage change is that found in Period 2 compared with Period 1.

▲ — —▲ = full term infants breathing air on each occasion (Table 1).
C - - - O = premature infants breathing air in Period 1 and 15% O_2 in Period 2 (Table 3).
● = full term infants breathing air in Period 1 and 15% O_2 in Period 2 (Table 2).

antly less than that of the full term infants (-8.5% in premature and -16.9% in full term infants). Secondly, it is noticeable that there is an increased fall in oxygen consumption in the premature infant with increasing age. Thus the regression of oxygen consumption on age shows that at 13 days of age the oxygen consumption on 15% O_2 has fallen by about 13%. This seems to suggest that there is a trend towards full term behaviour in this respect with the approach to the age of normal delivery.

Thirdly, some data possibly relevant to this difference between premature and full term infants are shown in Fig. 3, in which the percentage change of oxygen consumption in Period 2 vompared with Period 1 is plotted against the percentage change of minute volumes in these two periods. It will be noted that in full term infants breathing air on both occasions, the expected relationship between these two variables is found—i.e., with slight rises in minute volume there are slight rises in oxygen consumption and vice versa. Such a relationship also holds for the premature infants who breathed air in Period 1 and 15% O_2 in Period 2; as one might expect with a reduction in oxygen passing through the lungs the whole level of oxygen consumption

is depressed, but changes in oxygen consumption are still related to changes in volume of ventilation. In contrast, in the full term infants breathing 15% O_2 after air, we find no such relationship; now change in the amount of oxygen consumed is not directly related to change in the amount of oxygen passing through the lungs.

The first and second observations suggest that the full term infant faced by anoxia lowers its oxygen consumption more readily than does the premature. The third observation suggests the possibility that in the full term infant there may be some process at work whereby in anoxia lowering of oxygen consumption can be actively induced instead of passively accepted. It is not argued here that this suggestion is in any way proven, but any work which either establishes or refutes this hypothesis will materially advance our knowledge of the physiology of the new-born.

Implications

A low body temperature in a new-born baby is generally assumed to be due to immaturity of homoeothermic mechanisms. But the evidence presented here suggests that anoxia will decrease metabolic activity, and therefore ultimately lead to a fall of body temperature. Thus a low temperature in a new-born baby may be symptomatic of anoxia—evidence possibly of an adaptive process rather than lack of control. In cardiopulmonary disorders producing anoxia one can well imagine that a lowering of the metabolic rate is an indispensable condition of survival. Inability to shiver has often been cited as particular evidence of the immaturity of the new-born baby's temperature regulating mechanism. We would suggest that lack of shivering is necessary, if a fall in metabolism is to be used as a defence against anoxia.

Conversely, while the anoxic baby does not raise its temperature by shivering, this can be, and often is, achieved artificially by raising the environmental temperature. But increasing body temperature will tend to quicken cellular activity, and may therefore increase the demand for oxygen above the anoxic baby's capacity to supply it.

Summary

The oxygen consumption and carbon dioxide production have been measured in groups of babies breathing air followed by 15% oxygen.

During this mild hypoxia the oxygen consumption of full term and premature babies dropped by 17% and 9% respectively. There was only slight evidence of anaerobic metabolism during hypoxia.

Conclusion

Under the experimental conditions described here the newborn baby, unlike the adult, responds to hypoxia by lowering its energy production. Some of the implications of this have been briefly considered.

Métabolisme gaseux du nourrisson nouveau-né aspirant 15 % d'oxygène.

La consommation d'oxygène et la production d'acide carbonique ont été mesurées dans des groupes de bébés aspirant de l'air et ensuite 15 % d'oxygène. Lors de cette hypoxémie légère, la consommation d'oxygène chez les nourrissons nés à terme et chez les prématurés a diminué de 17 %, respectivement de 9 %. On a seulement constaté une faible preuve de métabolisme anaérobe pendant l'hypoxémie. Dans les conditions expérimentales décrites, le nourrisson nouveau-né, à l'opposé de l'adulte, réagit sur l'hypoxémie par une diminution de sa production d'énergie. Quelques unes des implications concernant ces symptômes ont été sommairement considérées.

Gasaustausch bei Neugeborenen bei 15 % Sauerstoffeinatmung.

Sauerstoffverbrauch und Kohlensäureausscheidung wurden bei einer Gruppe von Kleinkindern, welche Luft und darauffolgend 15 % Sauerstoff zu atmen erhielten, bestimmt. Während dieser milden Hypoxie fiel die Sauerstoffaufnahme bei vollreifen und vorzeitigen Neugeborenen um 17 %, beziehungsweise 9 % ab. Es bestanden nur geringfügige Anzeichen von anaerobem Stoffwechsel während der Hypoxie. Unter den beschriebenen Versuchsbedingungen reagiert das neugeborene Kind im Gegensatz zum Erwachsenen auf Hypoxie mit einer herabgesetzten Energieproduktion. Gewisse Folgerungen aus dieser Tatsache werden kurz betrachtet.

Metabolismo gaseoso del recién nacido inhalandó un 15 % de oxígeno.

El consumo de oxígeno y la producción de dióxido de carbono han sido medidos en grupos de bebés respirando aire y después 15 % de oxígeno. Durante esta hipoxia moderada, el consumo de oxígeno de los niños nacido a término y el de los prematuros, descendió con un 17 % y 9 % respectivamente. Solo hubo una leve apariencia de anaerobia metabólica durante la hipoxia. Bajo las condiciones experimentales descritas, el neonato, contrariamente a lo que sucede en el adulto, responde a la hipoxia disminuyendo su producción de energía. Se consagran breves consideraciones a la discusión de algunas inferencias.

Appendix I

Calculation of changes of energy production on 15 % oxygen after air

Weight of average full term baby (see Table 2) = 3.1 Kg.

Period 1. Breathing air.

Average oxygen consumption	= 1440 ml/hr
Average CO_2 production	= 1110 ml/hr
Average R.Q.	= 0.77

Period 2. Breathing 15 % oxygen.

Average oxygen consumption	= 1193 ml/hr
Average CO_2 production	= 1016 ml/hr
Average R.Q.	= 0.85

If the actual metabolism during Period 2 had continued at an R.Q. of 0.77, then with an oxygen consumption of 1193 ml/hr one would expect CO_2 production of 1193 × 0.77, which equals 920 ml/hr. In fact there was an excess of 96 ml (1016 − 920) of CO_2 displaced, if our assumption on p. 218 is correct, by lactic acid.

It is now necessary to estimate the relative calorific value of a molecule of CO_2 produced by the aerobic breakdown of glucose compared with the calorific value of a molecule of CO_2 produced by anaerobic glycolysis. Taking the values quoted by Burton (Table 11) of Krebs and Kornberg (1957), we have:—

1 Glucose $\rightarrow$ 6 CO_2 + 6 H_2O	= 686.5 K. Calories
1 Glucose $\rightarrow$ 2 Lactate + 2 Hydrogen	= 47.4 K. Calories
$\therefore$ 1 CO_2 from aerobic breakdown of glucose	= 686.5/6 = 114.4 K. Calories
1 CO_2 from anaerobic glycolysis	= 47.4/2 = 23.7 K. Calories.

We have, therefore, that 1 CO_2 from anaerobic glycolysis gives $23.7/114.4 \times 100\%$ of the energy obtained from 1 CO_2 produced by oxygenation = 20.7%.

Referring to the average full term baby we find that by aerobic glycolysis on 15% oxygen he produces $920/1110 \times 100$ = 82.9% of the total energy production when breathing air.

Also anaerobically there is $96/1110 \times 20.7/100 \times 100$ = 1.79% of the total energy production on air

Hence, total metabolism on 15% oxygen = 82.9 + 1.79 = 84.7% of the total energy production on air.

From these calculations we conclude that the normal baby has a deficit of energy production of about 15.3% when breathing 15% oxygen mixture.

There are a number of assumptions that are implicit in this calculation.

1. It is assumed that with 15% oxygen the baby does undertake anaerobic glycolysis.

2. That within about ten minutes of starting to breathe this mixture the baby had reached an equilibrium state, so that the lactate being produced within the cells was coming into contact with the bicarbonate of the extracellular fluid, and thus the carbon dioxide being produced reflects the rate of lactate production. Some credence is lent to this point of view by the babies who received 15% oxygen for two successive periods (see Table 4), when we find that the rate of oxygen consumption and carbon dioxide production had changed only very slightly during the second period on 15% oxygen compared with the first.

3. It is also assumed, as stated in the calculation, that the other metabolic pathways of the baby remain unaltered during the period when a low oxygen mixture is being breathed.

It is appreciated that large assumptions have been made in the suggested calculation which is set out above, and it is probable that the rate of lactate production may be higher than is evidenced by the rise of R.Q. However, it seems unlikely that these uncertainties could in any way add up to account for the overall loss of energy production which appears to occur, and thus we must assume that there is a genuine fall of energy production under these circumstances.

Appendix II

A previous error, and a note on statistical techniques

It may be noted that there are slight discrepancies (never as much as 1%) between the results reported in the previous paper and those reported in Table 3. The slight errors have been found when all the previous results were recalculated for the present report. For example, premature baby No. 3 was previously stated to have an oxygen consumption of 359 ml of oxygen per Kg per hour, but recalculation shows 361 ml to be a more accurate figure. Our analyses would not differentiate 2 ml in 350, but as these results are to be compared with others on the same basis, it would seem desirable not to perpetuate a previous arithmetical error.

When a comparison was being made with paired results from each baby the "*t*" test on the *differences* between the paired results has been used to test the significance of the differences found.

$$t = \frac{\text{mean of differences}}{\text{standard deviation of differences}} \times \sqrt{\text{number of observations.}}$$

This technique does not lend itself conveniently to illustration, and for this reason the diagram in Fig. 1 shows the mean on Period 1 (shown as 0% for all babies) and the percentage change from that mean is illustrated for Period 2. It is found (by the appropriate *t* test mentioned above) that if the confidence limit in the experimental Period 2 does not overlap zero, then in fact the *t* test is always significant. Thus the diagram is a reasonably simple visual aid to reading off the significance of results.

The other statistical techniques, as this one, are standard in any elementary statistical text book.

Acknowledgement

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Addendum

After submitting the manuscript we have read the paper of James & Rowe (1957). They find that even in babies as old as eleven days breathing low oxygen mixtures causes a marked decrease in femoral arterial oxygen saturation (70 and 75 per cent saturation in one baby breathing 15 per cent oxygen). They attribute this to a re-establishment of the foetal pattern of circulation. Our suggested figure for arterial oxygen saturation of 85 per cent may well be too high, at least for the lower half of the body.

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Hyperbilirubinemia and ABO Hemolytic Disease in Newborn Infants of Diabetic Mothers

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The cause of the high incidence of neonatal deaths among infants of diabetic mothers (cf. Miller) still remains an unsolved problem. Many of the characteristic features of these infants during the first few days of life can be ascribed to a functional immaturity of the organism, but others cannot be satisfactorily explained in this manner. Miller, Johnson & Durlacher were the first to call attention to the fact that some of the clinical features resemble those encountered in hemolytic disease of the newborn. In both conditions the infants may show marked edema, erythroblastosis and extramedullary hematopoiesis (Miller & Wilson).

The purpose of this communication is to report a high incidence of hyperbilirubinemia in newborn infants of diabetic mothers. The cause of excessive bilirubinemia in these infants may be partly interpreted in terms of functional immaturity, i.e. there is an extension to what is called physiologic jaundice. However, in many cases, the intense accumulation of bilirubin finds its explanation in a remarkably high incidence of ABO hemolytic disease. In all investigated A–O heterospecific pregnancies complicated by diabetes, the newborn infant exhibited features characteristic of hemolytic disease.

Material

Twenty-nine consecutive newborn infants of diabetic mothers, transferred from the obstetrical departments of various hospitals, were studied. In all instances the duration of diabetes exceeded one year, in the majority the duration was more than five years. Two pregnancies were complicated by toxemia. In 11 instances the infant was the first offspring. In the remaining cases the number of earlier pregnancies was variable; one infant was the seventh child in the family. Among the multiparas there was a high incidence of previous fetal deaths. One of the mothers was Rh-isoimmunized.

A great number of the pregnancies was terminated by caesarean section. Two infants were very prematurely born, one of them spontaneously, the other following caesarean section (gestational age 32 and 33 weeks respectively). Thirteen pregnancies were interrupted by caesarean section in the 35th or 36th week. Fourteen infants can be considered to be born at term, i.e. with a fetal age of more than 36 weeks, 6 of these infants were born by caesarean section.

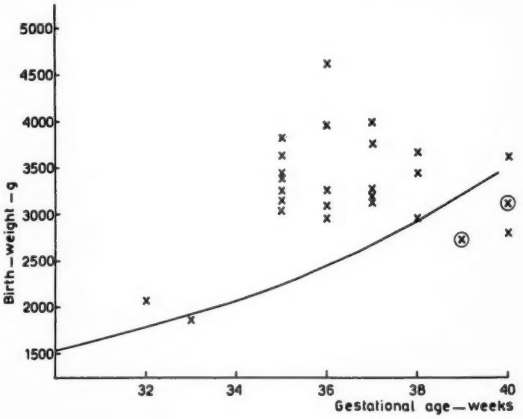

Fig. 1. Showing the birth weight of the infants of diabetic mothers in relation to the gestational age. The line represents the normal fetal weight gain during the last part of fetal life. With the exception of a few cases, the infants were found to be much heavier than would have been expected for normal newborn infants. The two infants indicated by a circle around the cross were born after a pregnancy complicated by toxemia.

Physical examination during the first day of life revealed, in most of the infants, features typical of the syndrome characteristic of infants of diabetic mothers. With few exceptions, the body weight was considerably higher than in other newborn infants (Fig. 1). No real congenital malformations were noted, but transient cardiac murmurs where heard in several cases. The infants showed a varying degree of edema. There was a rather high incidence of respiratory insufficiency with frequent attacks of cyanosis during the first one or two days of life. For this reason oxygen therapy was instituted in some cases. The period of such treatment never exceeded 3 days and the concentration was always kept below 40 per cent. To prevent hypoprothrombinemia, 5 mg of water-soluble vitamin K was given to all infants. No infants received sulfisoxazole (Gantrisin).

Both the very immature babies expired, one from the hyaline membrane syndrome, the other at an age of three days with signs suggestive of kernicterus. The third fatal outcome occurred at an age of one week in a full-term infant who had developed symptoms of brain damage on the third day of life. In both patients with possible kernicterus, necropsy was denied. The rest of the infants survived, the mortality rate in this series thus being about 10 per cent. With the exception of one child who exhibited some signs of brain damage (lethargy), there were no sequelae.

Methods

Venous blood for the determination of serum bilirubin or for the measurement of radioactivity was obtained from the internal jugular or femoral veins. Serum bilirubin was determined according to the method of Malloy & Evelyn, as modified by Ducci & Watson. The survival of the red cells was measured with the aid of the labeled chromium method (Gray & Sterling). The technique of labeling the red cells in vivo was applied (Sutherland & McCall). In each patient investigated about 15 microC was injected intravenously as sodium bichromate. The serological investigations were carried out at the State Rh-laboratory, Stockholm, under the direction of Prof. B. Broman.

TABLE 1

Maximum level of serum bilirubin attained during the neonatal period in 29 infants of diabetic mothers.

Maximum level attained mg per 100 ml	Number of cases		
	Gestational age 32–34 weeks	Gestational age 35–36 weeks	Gestational age 37–40 weeks
Below 10	–	–	4[a]
10 to 18	1	4	6
Over 18	1	9	4

[a] One of the infants belonging to this group has been excluded from further tabulation because of Rh-isoimmunization (maximum bilirubin level attained 7.2 mg per 100 ml).

Results

Entire material.—The maximum serum bilirubin levels for the whole material are given in Table 1. In this table the infant of the Rh-isoimmunized mother is included. Since, however, this infant was found to be Rh-positive and isoimmunized, it has been excluded from further discussion. Curiously enough, this infant belonged to those with the mildest bilirubinemia.

Infants without evidence of hemolytic disease.—Daily total serum bilirubin values of such infants of diabetic mothers where the serological investigation disclosed no heterospecific pregnancy are given in Tables 2–4. No primary cause could be found for the hyperbilirubinemia. Only a trace of direct reacting bilirubin was found even in these infants who were most heavily jaundiced; thus obstructive jaundice was excluded.

One of the 12 full-term infants attained a maximum serum bilirubin concentration above 30 mg per 100 ml and in two additional infants it rose above 18 mg per 100 ml (Table 2). From Tables 1 and 3, and Fig. 2 it is evident that infants who were just at the limit of being premature as judged from the fetal age alone showed a more pronounced tendency to become hyperbilirubinemic than those born at term. This finding is in accordance with repeated observations that premature infants are more prone to have high serum bilirubin levels than those born at term (cf. Crosse, Meyer & Gerrard). Five of these 9 infants had bilirubin levels higher than 18 mg per 100 ml. Finally, in Table 4 the two very premature infants have been included. One of these infants had a serum bilirubin of 23.5 mg per 100 ml on the third day of life, the other a level of 16.8 mg per 100 ml. In both these infants further accumulation of bilirubin might have occurred if the outcome

TABLE 2

Daily total serum bilirubin levels (mg per 100 ml) in twelve infants of diabetic mothers. Gestational age 37–40 weeks. No evidence of hemolytic disease of the newborn.

Patient	Birth wt.	Hemoglobin[a] g per 100 ml	Day 1	2	3	4	5	6	7	8–9	10–12
1	3190	15.3		13.4	19.1[b]	18.8		9.2	[c]		
2	3660	23.6		13.5		22.4	20.3		19.4	15.0	
3	2950	20.8		2.5		4.8		3.7			
4	3240	20.0		4.9		11.4		8.2			
5	3750	20.2		9.3				14.9			
6	3100	17.0		11.0		20.2		30.6			7.2
7	3980	19.4	0.5	7.5	10.8						
8	3090	15.5		5.4	11.8	10.2					
9	2790	19.8			10.0	13.1		9.5			
10	3430	20.0			3.1						
11	3620	22.6		9.4	13.2	12.5		8.2			
12	4950	23.6	0.8	6.3			4.8				

[a] Hemoglobin was determined first day of life (capillary blood).
[b] Indicates exchange transfusion.
[c] Indicates infant died, Case 1, Table 5.

TABLE 3

Daily total serum bilirubin levels (mg per 100 ml) in nine infants of diabetic mothers. Gestational age 35–36 weeks. No evidence of hemolytic disease of the newborn.

Patient	Birth wt.	Hemoglobin[a] g per 100 ml	Day 1	2	3	4	5	6	7	8–9
			Total serum bilirubin (mg per 100 ml)							
13	3240	15.8		12.0	19.2	20.2				
14	3440	20.2		12.7		18.4				
15	3130	19.6		8.1		18.3		14.1		
16	3950	13.1		7.2		12.6		11.2		
17	5180	23.2		15.3		19.8	24.0[b]	18.6	16.2	10.1
18	3400	18.4		3.8	9.4	14.4	16.1	16.4	15.6	11.7
19	3260	16.2		7.3		11.7			7.0	
20	3150	17.6		5.9		14.0		17.6	17.1	15.6
21	3820	22.4		10.0		19.0			19.4	13.8

[a] Hemoglobin determined first day of life, capillary blood.
[b] Indicates exchange transfusion.

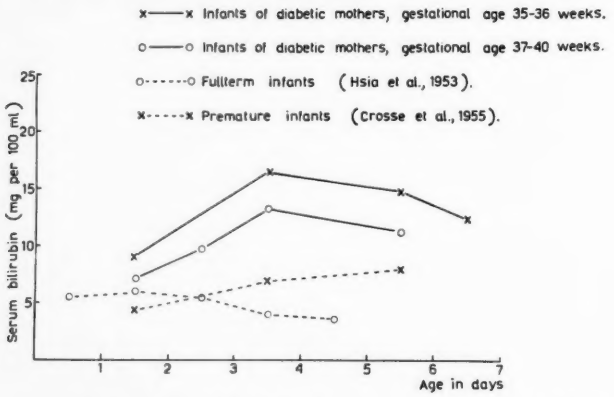

Fig. 2. Comparison of daily average bilirubin levels in two groups of infants of diabetic mothers without evidence of hemolytic disease, of full-term infants according to Hsia *et al.* (1953), and of prematures (Crosse *et al.*).

had not been fatal at such an early stage since in infants with a birth weight of less than 2000 g the serum bilirubin is usually still increasing on the sixth day of life (cf. Crosse *et al.*).

Fig. 2 shows the average daily bilirubin values during the first day of life of two groups of infants of diabetic mothers without hemolytic disease (cf. Tables 2 and 3) compared with normal newborn infants (Hsia, Allen, Diamond & Gellis) and with prematures (Crosse *et al.*). In both groups of infants of diabetic mothers the peak levels were attained on the fourth day of life, thus somewhat later than in normal newborn infants but not as late as in prematures. In the group of infants of diabetic mothers born at term, the average of the daily serum bilirubin levels during the first days of life was much higher than in normal newborn infants (cf. also

TABLE 4

Daily total serum bilirubin levels (mg per 100 ml) in two infants of diabetic mothers. Gestational age 32–34 weeks. No evidence of hemolytic disease of the newborn.

Patient	Birth wt. g	Hemoglobin[a] g per 100 ml	Day 1	Day 2	Day 3
22	1860	16.5			23.5[b]
23	2070	20.6		10.2	16.8[b]

[a] Hemoglobin was determined on capillary blood first day of life.
[b] Indicates infant died. Necropsy in Case 22 showed hyaline pulmonary membranes. Case 23 expired with signs of brain damage, necropsy was denied.

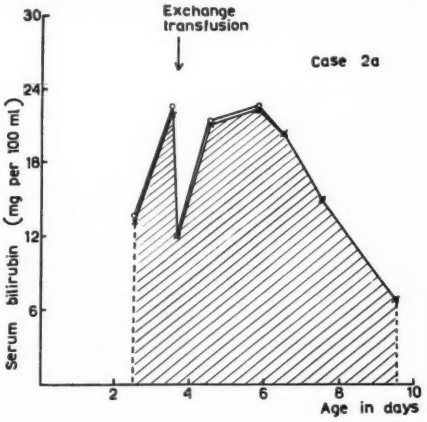

Fig. 3. Daily serum bilirubin levels and effect of replacement transfusion in an infant of a diabetic mother with hyperbilirubinemia but without hemolytic disease (Case 2). The shaded area indicates indirect reacting bilirubin, the rest is direct reacting. After the exchange transfusion there was a rapid rebound of the bilirubin concentration in the serum.

Davidson, Merrit & Weech), and even the levels attained in prematures were exceeded.

In order to investigate whether the intense hyperbilirubinemia which developed in some of the infants might be explained solely in terms of an inefficient excretory function of the liver, the survival of the red cells was determined in three cases. This was done to exclude the possible existence of an added load of bilirubin due to an abnormal hemolytic rate. Such an investigation was considered to be necessary, especially since many of the infants had been given extra oxygen because of respiratory insufficiency and this treatment may cause increased hemolysis (cf. Bakker). By tagging the patient's own red cells with radioactive chromium, the mean life span was calculated to be about 90 days (cf. Fig. 4, Case 11). This result is in agreement with the finding of Hollingsworth, that red cells from newborn infants survive for up to 80–90 days when injected into a normal recipient.

To prevent the development of kernicterus, three of those infants who rapidly attained high serum bilirubin concentrations were treated with one exchange transfusion in order to remove bilirubin. In two of these infants the fetal age exceeded 36 weeks; in the remaining one it was 36 weeks. Some complementary data of these patients are collected in Table 5. In all three patients there was a rapid rebound of the serum bilirubin with a rise up to the pretreatment level within 12 hours (Fig. 3), although the efficiency of the exchange transfusions was increased by replacing up to a total volume of 600 ml (cf. Stempfel, Broman, Escardó & Zetterström). This may be explained in terms of a rapid withdrawal of bilirubin from the tissues at a time when the excretory capacity of the liver is low. As soon as bilirubin excretion is increased, the level rapidly falls.

TABLE 5

Clinical and laboratory findings in three markedly hyperbilirubinemic infants of diabetic mothers without evidence of hemolytic disease of the newborn. (Italicized figures represent values obtained immediately after exchange transfusion.)

	Age days	Hemoglobin g per 100 ml	Reticulocytes, per cent	Serum bilirubin mg per 100 ml Direct	Total	Progress
Case 1						
Gestational age 37	1	15.5				Severe respiratory dis-
weeks. Maternal blood	2	18.4	0.5	0.3	13.4	tress first day of life.
group A Rh (+). In-	3				19.1	Fourth day of life
fant's blood group	3½			0.8	18.8	signs of brain damage.
0 Rh (+).	3½			*0.4*	*9.4*	Expired on 7th day
	4				18.8	(cerebral symptoms).
	6				9.2	Autopsy denied.
Case 2						
Gestational age 38	1	23.6	3			Uncomplicated
weeks. Maternal blood	2			0.3	13.5	course.
group A Rh (+). In-	4	22.7		0.3	22.4	
fant's blood group	4½			0.3	20.3	
0 Rh (+).	4½			0	*11.8*	
	5			*0.3*	20.3	
	7				19.4	
	8				15.0	
Case 18						
Gestational age 36	1	23.2	4	0.4	15.3	Lethargy from 4th to
weeks. Maternal blood	3				19.8	7th day; thereafter
group A Rh (+). In-	4	22.2			24.4	progressive improve-
fant's blood group	4½			0.7	24.0	ment.
A Rh (+).	4½			*0.7*	*18.6*	
	5				16.2	
	7			0.5	10.1	

In all instances was the maternal Coombs' reaction indirect negative and in the infant the Coombs' reaction direct negative.

According to criteria given by Crosse *et al.*, two of the infants showed features related to kernicterus (Cases 1 and 23), but since autopsy was not permitted the diagnosis could not be established. In one of these infants exchange transfusion was performed (Case 1). One of the infants in whom the bilirubin level rose to 30.6 mg per 100 ml remained quite healthy. This confirms the common observation that some infants tolerate extraordinarily high concentrations of bilirubin without developing demonstrable effect:

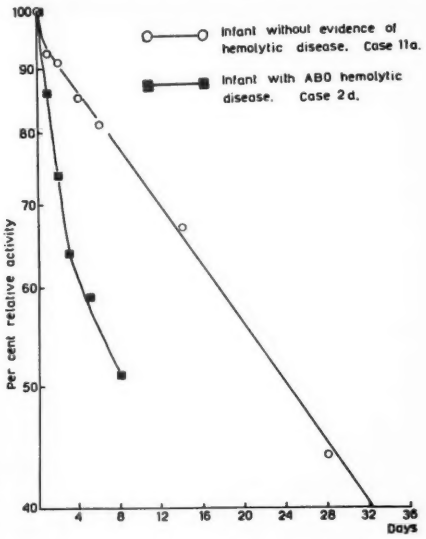

Fig. 4. Rate of disappearance of radioactive chromium after *in vivo* labelling of the erythrocytes in one infant of a diabetic mother with hyperbilirubinemia without hemolytic disease (Case 11); and in one with ABO hemolytic disease (Case 25). The mean erythrocyte survival in the infant without hemolytic disease was normal (80–90 days). In the patient with ABO hemolytic disease it was shortened.

others, especially prematures (Meyer), may develop kernicterus at comparatively low plasma levels of bilirubin.

Infants with evidence of ABO hemolytic disease.—Some clinical data of those infants of diabetic mothers with features consistent with a diagnosis of ABO hemolytic disease of the newborn are listed in Table 6. All cases were due to anti-A antibodies. The criteria of diagnosis (i.e. heterospecific pregnancy and early onset of intense hyperbilirubinemia) were more or less those given by Crawford, Cutbush & Mollison, and by Levine, Vogel & Rosenfield. The presence of antibodies of the immune type in maternal serum, microspherocytosis with varying red cell diameter and decreasing hemoglobin levels, were considered to be additional evidence. The antiglobulin test of Coombs was negative in all patients. Since, however, definite criteria of ABO hemolytic disease are inadequate, such a diagnosis may be questionable in many cases. In Case 25 the diagnosis of ABO hemolytic disease seems a little dubious. However, the measurement of the survival time of the infant's red cells has provided clear evidence of an abnormally rapid hemolytic rate. Fig. 4 shows the calculated mean life span as about 30–35 days. The results thus are in agreement with those obtained when the erythrocyte survival has been determined with the aid of the Ashby technique in ABO hemolytic disease (Boorman, Dodd & Trinick; Mollison & Cutbush).

Replacement transfusion was performed in two of the infants with hemo-

TABLE 6

Clinical and laboratory findings in five infants of diabetic mothers presenting features of ABO hemolytic disease. (Italicized figures represent values obtained immediately after exchange transfusion.)

	Age days	Hemoglobin g per 100 ml	Reticulocytes, per cent	Serum bilirubin mg per 100 ml Direct	Total	Progress
Case 24						
3rd child. Gestational age 36 weeks. Maternal blood group 0 Rh(+). Infant's blood group A Rh(+). In the serum from the mother anti-A and anti-B of immune type. Microspherocytosis.	2	17.4	5.0	1.3	12.8	Respiratory distress first day of life. Definite symptoms of brain damage when 5–15 days old, improved successively.
	3			1.0	18.5	
	4	15.2		1.3	22.7	
	4½			*0.8*	*9.2*	
	5			0.9	15.3	
	6	15.4		0.8	13.6	
	20	11.8				
Case 25						
First child. Gestational age 39 weeks. Maternal blood group 0 Rh(+). Infant's blood group A Rh(+). In the serum from the mother anti-A of immune type.	1	21.2	3.0		8.0	No neurologic symptoms
	2				18.8	
	3	19.4			19.7	
	4				22.4	
	5				15.6	
Case 26						
Second child. Gestational age 36 weeks. Maternal blood group 0 Rh(+). Infant's blood group A Rh(+). In the serum from the mother anti-A of immune type.	1	14.0	7.3	0.3	9.2	Moderate respiratory distress first day of life. No neurologic symptoms.
	3	15.5		1.1	25.3	
	6	13.1	0.5	0.7	4.7	
Case 27						
Second child. Gestational age 35 weeks. Maternal blood group 0 Rh(+). Infant's blood group A Rh(+). In the serum from the mother anti-A of immune type. Microspherocytosis.	1	15.8	1.8			Lethargy from 4th to 9th day; thereafter progressive improvement. Asymptomatic when last seen at 1 month of age.
	2				17.5	
	5	15.3			26.9	
	6	15.9			25.9	
	8	15.0			20.2	
	12	14.4			10.5	
	22				1.8	
Case 28						
3rd child. Gestational age 35 weeks. Maternal blood group 0 Rh(+). Infant's blood group A Rh(+). In the serum from the mother anti-A of immune type. Microspherocytosis.	2	25.0	6.3		15.0	No symptoms of brain damage.
	4	18.2		0.8	27.6	
	4½			0.8	29.1	
	4½			*1.3*	*12.8*	
	5	17.3		1.2	25.2	
	5½			0.6	25.2	
	5½			*0.8*	*11.1*	
	6			0.8	19.6	
	8			0.6	15.4	
	10	11.2		0.2	7.6	

Direct Coombs' test on the infants' red cells was negative in all five cases.

lytic disease due to anti-A antibodies. In one infant the exchange transfusion was repeated. Two of the infants were lethargic when the serum bilirubin attained its peak level; in one of these infants brain damage may have persisted.

Discussion

Since the recognition that heavily jaundiced infants may develop kernicterus independent of the etiology of the hyperbilirubinemia (Zuelzer & Mudgett), considerable interest has been focused upon states of excessive bilirubinemia during the neonatal period. A tendency towards very high serum bilirubin levels is particularly marked in prematures (Crosse *et al.*) but such levels may also be found in apparently healthy newborn full-term infants (Brown & Zuelzer).

Our data demonstrate that newborn infants of diabetic mothers are prone to develop hyperbilirubinemia. Since the excretion of bilirubin is preceded by its conjugation with glucuronic acid within the liver (Billing, Cole & Lathe; Schmid; Carbone & Grodsky) it seems logical to assume that the efficiency of the enzyme systems involved is low at birth. Such a delay in the development of this enzyme system has been suggested by Brown on the basis of glucuronide excretion studied in newborn infants and more detailed studies of this conjugating system in guinea pigs. This was not confirmed by Lacson & Waters who determined urinary hexuronic acid in newborn infants. The reason why infants of diabetic mothers should be handicapped by immaturity of the liver remains obscure. Since respiratory insufficiency is very common in newborn infants of diabetic mothers, it may be of significance that Brown & Zuelzer thought that perinatal hypoxia may predispose to the development of neonatal hyperbilirubinemia. More recent investigations by Miller & Reed also showed a direct relationship between respiratory distress and degree of bilirubinemia in newborn infants.

There was an extremely high frequency of ABO hemolytic disease in this material. In fact, there was evidence of this disorder in all A–O heterospecific pregnancies. This finding seems remarkable, since ABO hemolytic disease is considered to be rather rare. According to Copeland, Verys & Ullery, it is diagnosed in about 0.30 per cent of all live births. However, many cases of this disorder may be very mild and thus remain undiagnosed. The true incidence may be higher and it has been suggested that it is numerically about equal to that due to Rh-isoimmunization (Copeland *et al.*). This is still much lower than the 18 per cent in this group. This high incidence is difficult to explain. The suggestion by Zuelzer & Kaplan that a placental defect is necessary for the development of ABO hemolytic disease of the newborn may have some bearing in this connection.

The results of the present study seem to indicate that the presence of ABO hemolytic disease should be considered in heterospecific pregnancies complicated by diabetes.

The aim of therapy in neonatal jaundice is the prevention of kernicterus. Since much remains to be clarified about the individual susceptibility to high serum bilirubin levels, an exact guide to replacement transfusion is lacking. In the present material, exchange transfusions were performed in three infants. Despite this, one of these infants died with symptoms suggesting kernicterus. The total protein concentration of the cerebrospinal fluid may serve as an indicator of the functional state of the blood–brain barrier system (Ernster, Herlin & Zetterström). In view of the above hypothesis, it is noteworthy that this infant even on the fifth day of life had a very high total protein concentration in the cerebrospinal fluid (221 mg per 100 ml).

Summary

In 29 consecutive cases of newborn infants of diabetic mothers, the serum bilirubin levels during the neonatal period have been studied. These infants are predisposed to the development of hyperbilirubinemia. The average bilirubin levels for the group exceeded those of normal newborn infants. In the majority of these infants, hemolytic disease or other causes of jaundice could be excluded. The hyperbilirubinemia was considered to be the result of functional immaturity of the liver.

The diagnosis of ABO hemolytic disease was made in 5 of the patients. The high frequency of this complication seems to indicate that the development of this disorder is favoured in pregnancies complicated by diabetes.

L'hyperbilirubinémie et la maladie hémolytique ABO chez les nourrissons nouveaux-nés de mères diabétiques.

Dans vingt-neuf cas consécutifs, on a étudié les taux du sérum bilirubine chez des nourrissons nouveaux-nés de mères diabétiques, pendant la période néonatale. Ces nourrissons sont prédisposés au développement d'hyperbilirubinémie. Les taux moyens de bilirubine constatés dans ce groupe dépassent ceux trouvés chez des nouveaux-nés normaux. Chez la plupart de ces nourrissons, une maladie hémolytique ou d'autres causes donnant lieu à une jaunisse peuvent être exclues. L'hyperbilirubinémie est considérée d'être le résultat d'une immaturité fonctionnelle du foie. Parmi les maladies diagnostiqués, il y a 5 d'entre eux chez qui on a constaté une maladie hémolytique ABO. La fréquence élevée de cette complication semble indiquer que le transfert placentaire d'anticorps « anti-A » est favorisé dans des cas de grossesse compliquée par un diabète.

Hyperbilirubinämie und ABO hämolytische Krankheit bei neugeborenen Kindern zuckerkranker Mütter.

Bei 29 aufeinanderfolgenden Fällen von neugeborenen Kindern diabetischer Mütter wurden die Serumbilirubinspiegel während der Neugeborenenperiode studiert. Diese Kinder zeigen eine Neigung zur Entwicklung von Hyperbilirubinämie. Die durch-

schnittlichen Bilirubinspiegel dieser Gruppe übertrafen die bei normalen Neugeborenen beobachteten. Bei der Mehrheit dieser Kinder konnten hämolytische Krankheit oder andere Ursachen der Gelbsucht ausgeschlossen werden. Die Hyperbilirubinämie wurde als Ausdruck einer funktionellen Unreife der Leber aufgefasst. Die Diagnose der ABO hämolytischen Krankheit wurde bei 5 unter den Patienten gestellt. Die hohe Frequenz dieser Verwicklung scheint darauf hinzuweisen, dass bei mit Diabetes komplizierten Schwangerschaften eine Übertragung von anti-A Antikörpern auf dem Wege der Plazenta begünstigt wird.

La hiperbilirrubinemia y la enfermedad hemolitica ABO en el neonato de madre diabética.

En veintinueve casos sucesivos de recién nacidos, hijos de madres diabéticas, han sido estudiados los niveles séricos de la bilirrubina, durante la época neonatal. Estos niños están predispuestos al desarrollo de hiperbilirrubinemia. El promedio de los niveles bilirrubínicos de este grupo excedió los de los neonatos normales. En la mayoría de estos niños, pudieron excluirse la enfermedad hemolítica u otras causas de ictericia. Se consideró que la hiperbilirrubinemia resultaba de inmadurez funcional hepática. El diagnóstico de la enfermedad hemolítica ABO fué establecido en cinco de los pacientes. La elevada frecuencia de esta complicación parece indicar que la transferencia placentaria de anticuerpos A está favorecida en los embarazon complicados con diabetes.

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Prothrombin and Proconvertin in the Newborn and During the First Year of Life[1]

by HOLGER DYGGVE

The considerable lack of prothrombin normally found in the plasma of newborn infants was first described by Brinkhous, Smith & Warner (1) in 1937. In 1936 Dam, Schönheyder & Tage-Hansen (6) found that in vitamin K-deficient chicks the hemorrhagic tendency was due to a lack of prothrombin in the plasma. That vitamin K could raise the prothrombin level and check certain hemorrhages in newborn infants was first found in 1939 by independent investigations (7, 17, 28, 43).

Randall & Randall (34) in 1949 showed that besides the well-known prothrombin deficiency another coagulation factor must be lacking in the blood of newborn infants, since stored serum from adults containing neither fibrinogen, thrombin nor prothrombin, could by admixture to plasma from newborn infants with greatly prolonged prothrombin times shorten these times considerably.

During the last ten years the importance of proconvertin (Factor VII) for the coagulation of the blood has been established in the first place by Owren. Especially during treatment with dicumarol and similar drugs low concentrations of proconvertin are found in the plasma (see for instance Lund & Dyggve (25)), but this has also been described in the newborn (2, 8, 15, 21, 24, 26, 27, 29, 31). On the other hand proaccelerin (Factor V) was found to be normal or above normal in the newborn (3, 8, 15, 21, 29, 39, 42).

In this paper the result of prothrombin and proconvertin determinations immediately after birth and following injections of vitamin K are reported. The time of attainment of normal adult levels has also been investigated.

Methods

Quantitative determinations of plasma prothrombin and proconvertin were carried out with micro-modifications of Owren's original methods (Dyggve & Lund (12)). Prothrombin times were determined according to Larsen & Plum (23, 33). In a previous study (9) good correlation was found between the combined prothrombin–proconvertin concentrations and the prothrombin time when the latter was calculated as percentage.

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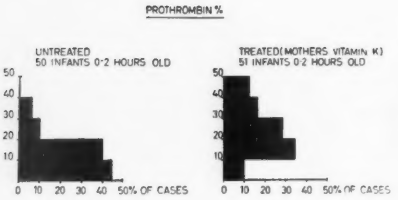
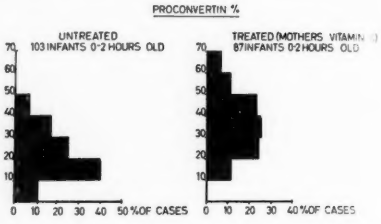


Fig. 1.



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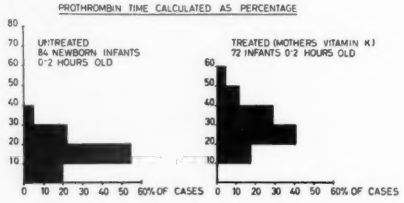

Fig. 3.

Results

Prothrombin concentrations were examined in 101 infants within two hours after birth. As shown in Fig. 1 very low levels were found especially when the mothers had not received vitamin K (mean: 12.6 %, range: 2–38 %). When vitamin K (usually 20 mg of menadione sodium bisulfite) was given orally 48–4 hours before delivery, the values were somewhat higher but still low (mean: 24.7 %, range: 6–50 %).

Fig. 2 shows the percentages of proconvertin in 190 infants less than two hours old. The level is somewhat higher than the prothrombin level, especially when the mothers received vitamin K as described above. Untreated: mean: 22.3 % (range: 6–50 %). Treated: mean: 38.7 % (range: 16–70 %).

In Fig. 3 the prothrombin times, calculated as percentage, are shown. Again the treated group has the highest values, but they are by no means as high as in normal adults. Since probably both prothrombin and proconvertin are measured by this method, the values are lying between those found by the quantitative estimation of either factor. Untreated: mean: 16.4 % (range: 5–37 %). Treated: mean: 31.1 % (range: 13–64 %). No significant difference was found between the average values of infants examined 0–1 hours and 1–2 hours after birth.

The average values of the two coagulation factors at birth, at the age of two days and at the age of 6 or 7 days are shown in Fig. 4. The groups comprise between 50 and 103 infants. No infants with birth weight below

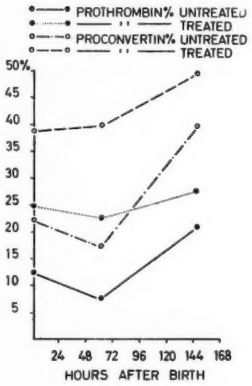

Fig. 4.

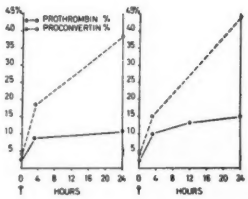

Fig. 5.

2000 g are included, since they were all given vitamin K immediately after birth. Infants with hemorrhages have also been excluded. It is seen that in the untreated infants a marked decrease in the level of both factors was found on the third day with a spontaneous rise at the end of the first week of life.

In the infants whose mothers received vitamin K before delivery the values at birth were higher than in the untreated infants, and the third day level was almost the same as the birth level, while the sixth day level was a little higher. The average proconvertin value was higher than the average prothrombin value both in the untreated and treated group.

Fig. 5 show examples of the influence of vitamin K (Synkavit 10 mg intramuscularly) given to infants with pronounced deficiency of both factors. Such experiments were carried out in 10 infants usually 2 or 3 days old. In all cases the rise in the proconvertin values occurred before and was more pronounced than that of the prothrombin.

In order to evaluate the normalization of the two coagulation factors 132 determinations were performed in 50 infants between the age of one week and two years. At the age of 4 months the proconvertin values were all normal as in adults (between 80 and 120%). The prothrombin values were more scattered and generally did not reach the normal adult level before the age of 10–12 months. Around the age of 6 weeks the prothrombin concentration was about 50%, but a value as low as 25% was found in a 10-week-old infant.

Discussion

There is no agreement concerning the question whether the prothrombin values of the newborn at birth can be raised by antenatal administration

of vitamin K. With the exception of infants with severe asphyxia at birth Larsen (22) found no difference in the average prothrombin time at birth (cord blood or heel blood) in treated and untreated cases. The same finding was made by Fiechter (13), Wespi (44), Gasser (16) and Fresh *et al.* (14). On the contrary Shettles *et al.* (37), Hellman *et al.* (18) and Snelling & Nelson (38) found higher values in the treated cases.

In my own examinations the average level of both prothrombin and proconvertin was somewhat higher in the treated than in the untreated infants and the lowest values tended to disappear in the treated group. The proconvertin values were higher than the prothrombin values both at birth and during the first week both in the treated and untreated cases. Fresh *et al.* (15) found that the level of the two factors was about equal at birth and through the first week. In disagreement with other investigators they found only minor influence of vitamin K upon the levels around the third day. Owen & Hurn (29), Larrieu *et al.* (21) and van Creveld *et al.* (2, 3) found the two factors to lie on about the same level, while Douglas & Davies (8) found the lowest concentration of proconvertin. On the contrary I found the proconvertin values to be higher than the prothrombin values.

Considerable disagreement also exists concerning the actual concentration of the two factors both at birth and later on in infancy. Loelinger & Koller (24) found 24% proconvertin and 28% prothrombin in a series of 33 cord bloods. Douglas & Davies found 38% and 82% respectively (42 cord bloods), Larrieu *et al.* 39% and 35% (8 cord bloods) and Fresh *et al.* 48% of both proconvertin and prothrombin (125 cord bloods). Especially the latter authors found wide individual variations (between 1% and 95% for both factors). Van Creveld *et al.* (2) examined the proconvertin content in the cord blood from 76 infants. The average value was 41%, varying from less than 10% to 100%. The proconvertin concentration on the second or third day was found to be 23 and 30% in untreated infants by these authors and 33% by Fresh *et al.* Douglas & Davies found it to be 15%, a value corresponding well with my own of 17.5%.

The results of the estimation of the prothrombin concentration on the third day are even more divergent: Fresh *et al.*, 27%; Owen & Hurn, 21%; van Creveld *et al.*, 30%; Douglas & Davies, 44%; present study, 7.5%. The great discrepancy must be due to differences in technique and standardization. A possible explanation for the much lower value in my series than that reported by others is, that while all our infants were breast-fed, only 4 of the 114 infants of Fresh *et al.* were breast-fed, and many infants were probably artificially fed in the other series. The higher prothrombin activity in the artificially fed newborn infants than in the breast-fed has been emphasized, for instance, by Salomonsen & Nygård (36) and Larsen (22). Dan-

et al. (5) found that cow's milk contains more vitamin K than woman's milk. The fact that breast feeding is often insufficient during the first days of life is also important in this connection. As a consequence all infants receiving cow's milk have been excluded from this investigation.

Only a few of our infants were asphyxiated at birth. They tended to have low values, but in some of them the concentrations were not below the average. Van Creveld *et al.* (2, 3) found that premature infants had lower concentrations of both prothrombin and proconvertin and responded much less after treatment with vitamin K than the full-term. Since all our infants with birth weight below 2000 g were given vitamin K, we have not been able to examine this question.

That vitamin K has a more rapid and more pronounced influence on the hypoproconvertinemia than on the hypoprothrombinemia of the newborn has not been reported previously.

That the prothrombin values do not become normal as in adults before the age of one year has been reported by Warner *et al.* (1) and by Plum (32). Fresh *et al.* (15) reported normal or almost normal values for both factors at the age of 8 to 10 weeks. Van Creveld *et al.* (2) examined the proconvertin content in a number of premature infants. Even in a group receiving vitamin K daily during the whole period of investigation the concentration did not exceed about 40% at the age of 5 weeks. In our infants the proconvertin concentrations reached normal values at the age of 3 to 4 months, whereas the prothrombin only became normal at 10 to 12 months.

In a previous study (11, 4) treatment of the mothers with vitamin K before delivery was found to result in a decrease in the number of hemorrhagic manifestations in the newborn infants. The most normal prothrombin times were found in the newborn infants when the mothers received repeated doses of vitamin K before delivery (10).

Summary

The concentration of both prothrombin and proconvertin in the plasma of newborn infants less than two hours old was somewhat higher in the cases where the mothers received a single oral dose of 20 mg of vitamin K 48 to 4 hours before delivery than in untreated infants. The values could however by no means be corrected to adult levels. The average prothrombin concentration rose from 13% to 22% and the proconvertin from 25% to 39%.

Daily examinations showed that in untreated breastfed infants a decrease in both coagulation factors occurred with a maximum around the third day. This was not seen in the treated cases. At the end of the first week the levels were somewhat higher than at birth especially in the treated group. The average proconvertin values were higher than those of prothrombin throughout the first week in treated as well as in untreated cases.

Intramuscular injection of 10 mg of Synkavit to untreated infants with low values resulted in a more rapid and more pronounced increase in the concentration of proconvertin than of prothrombin.

The proconvertin content was found to be normal at the age of 3 to 4 months, whereas the prothrombin values were more dispersed and only reached adult levels at the age of one year.

The use of vitamin K late in pregnancy is recommended in order to counteract the hypocoagulability and diminish the risk of hemorrhage in the newborn.

Prothrombine et proconvertine chez le nouveau-né et chez l'enfant lors de sa première année.

La concentration de la prothrombine, ainsi que celle de la proconvertine, présentes dans le plasma de 291 nourrissons nouveaux-nés, âgés de moins de 2 heures, sont un peu plus élevées dans les cas oú les mères ont reçu, 4 heures avant l'accouchement, une seule dose de Vitamine K 48 par voie orale, que celles trouvées chez les nourrissons non-traités. Les valeurs ne peuvent cependant nullement être redressées jusqu'à des taux adultes. La concentration moyenne de la prothrombine a augmenté de 13 % jusqu'à 22 %, et celle de la proconvertine de 25 % jusqu'à 39 %. Les examens journaliers ont montré que chez les nourrissons non-traités, il se produit, dans les deux facteurs de coagulation, une décroissance dont le maximum est aux environs du troisième jour. Cette diminution n'est pas constatée chez les nourrissons traités. A la fin de la première semaine, les taux sont quelque peu plus élevés qu'à la naissance, et ceci en particulier dans le groupe traité. Pendant toute la première semaine, les valeurs moyennes de proconvertine sont supérieures à celles de prothrombine, aussi bien dans les cas traités que dans ceux non-traités. L'injection par voie intramusculaire de 10 mg de Synkavit à des nourrissons non-traités avec des taux bas a eu comme résultat que la concentration de la proconvertine a augmenté plus rapidement et d'une façon plus prononcée que celle de la prothrombine. Il a été constaté que la teneur en proconvertine est normale à l'âge de 3 à 4 mois, tandis que les valeurs de prothrombine sont plus dispersées et atteignent les taux adultes, seulement à l'âge d'un an. L'administration de vitamine K, lorsque la grossesse est bien avancée, est à recommander, afin de contrebalancer l'hypocoagulabilité et de restreindre le risque d'une hémorragie chez le nouveau-né.

Prothrombin und Proconvertin bei dem Neugeborenen und während des ersten Lebensjahres.

Die Konzentration des Prothrombins als auch des Proconvertins im Plasma von 291 neugeborenen, weniger als 2 Stunden alten Kindern war ein wenig höher in den Fällen wo die Mütter eine einzelne peroral verabreichte Dose von 20 mg Vitamin K 48–4 Stunden vor der Entbindung erhielten, als in nicht so vorbehandelten Fällen. Die Werte konnten jedoch nicht bis zu dem bei Erwachsenen vorkommenden Spiegel verbessert werden. Die durchschnittliche Prothrombinkonzentration stieg von 13 % auf 22 %, die des Proconvertins von 25 % auf 39 % an. Täglich durchgeführte Untersuchungen zeigten, dass bei nicht vorbehandelten Kindern ein Abfall in der Konzentration beider Gerinnungsfaktoren erfolgte, mit einem Maximum am dritten Lebenstag. Dieser wurde in den behandelten Fällen nicht beobachtet. Am Ende der ersten Woche waren die Spiegel einigermassen höher als zur Zeit der Geburt insbesondere bei der vorbehandelten Gruppe. Die durchschnittlichen Proconvertinwerte waren die ganze erste Woche hindurch in vorbehandelten sowohl als nicht vorbehandelten Fällen höher als die Prothrombinwerte. Intramuskuläre Injektion von 10 mg Synkavi

bei nicht vorbehandelten Kindern mit niedrigen Werten hatte eine schnellere und ausgesprochenere Steigerung der Proconvertinkonzentration zur Folge als der Prothrombinkonzentration. Der Proconvertingehalt war, so wurde gefunden, im Alter von 3–4 Monaten normal, während die Prothrombinwerte zersplittert waren und Erwachsenenspiegel erst am Ende des ersten Jahres erreichten. Es wird empfohlen, Vitamin K in den späteren Stadien der Schwangerschaft zu verabreichen, um der herabgesetzten Gerinnungsfähigkeit beim Neugeborenen entgegenzuwirken und die Gefahr von Blutungen zu verringern.

Las protrombina y proconvertina en el recién nacido asi como en el primer año de la vida.

La concentración de ambas protrombina y proconvertina en el plasma de 291 recién nacidos de menos de dos horas de edad, se manifestó levemente más elevada en los casos de recibir las madres una sola dosis oral de 20 mg de vitamina K 48 a 4 horas antes del parto, que en los niños no tratados. Sin embargo, no pudieron corregirse los valores en ningun modo hasta los niveles adultos. El promedio de la concentración protrombínica ascendió del 13 al 22 % y el de la proconvertina, del 25 al 39 %. El examen diario permitió comprobar que, en los niños sin tratar, se presentaba un descenso en ambos factores de coagulación, acusando un máximo alrededor del tercer día. Esto no fué observado en los casos tratados. Al final de la primera semana, los niveles eran algo más elevados que al nacer, especialmente en el grupo tratado. El promedio de los valores de la proconvertina era más elevado que el de la protrombina, durante el transcurso de la primera semana, tanto en los casos tratados como en los sin tratar. La inyección intramuscular de 10 mg de *Synvavit*, en los niños no tratados que presentaban valores inferiores, resultó en un aumento más rápido y más pronunciado en la concentración de proconvertina que en la de protrombina. Se observó que el contenido de proconvertina era normal a la edad de 3 a 4 meses, mientras que los valores protrombínicos estaban más dispersados y solo alcanzaban los niveles adultos a la edad de un año. Se recomienda el uso de la vitamina K en la fase final del embarazo con objeto de contrarrestar la hipocoagulabilidad y disminuir el peligro de hemorragia en el recién nacido.

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Mysoline and Meprobamat in Cerebral Palsy

by P. PLUM and K. SPARUP

In the Department of Pediatrics, The University Hospital, Copenhagen, as elsewhere, medical treatment has been attempted in cerebral palsy. Torben Jersild (1) in 1950 described the good effect of Parpanit in 4 cases and Madsen, Lauersen & Ugland (2) in 1951 recorded the results of curare treatment. Although according to these and other communications an effect has been achieved in certain cases, the general impression gained in this department concerning medical treatment of cerebral palsy has been negative.

Rigidyl, Peragit, Diamox, Amidryl, Prostigmine, Benadryl, Mestinon, Phenantoin, Phenemal and Chlorpromazine have all been employed without convincing effect.

During recent years, communications (4, 5) have been published concerning the good effect of Meprobamat in cerebral palsy, particularly as regards athetosis. The authors of the present paper have arrived, to a certain extent, at a similar result but the reason for the publication of this communication is that we are of the opinion that another substance, viz. Mysoline, has such a good effect on athetosis that we have become somewhat more optimistic regarding the possibilities for medical treatment of cerebral palsy. A brief account of our preliminary observations will therefore be given together with an account of the results to date.

Mysoline

Case 1.—A boy aged 13 years suffering from torsion spasm. Asphyxia for 1–2 hours after birth. Severe icterus neonatorum lasting for 2 months but no blood type incompatibility and on examination now no immune antibodies could be demonstrated in the mother. The patient is able to speak quite well, he attends an ordinary school and is able to perform practically all normal movements but is handicapped by continual spasm, suggestive of continual torsion spasm. Ligature of the choroid artery on both sides at the age of 11 years did not lead to any clinical improvement nor did

medical treatment (Phenemal, Parpanit, Rigidyl, Peragit and Nembutal). One and a half years ago, Mysoline 125 mg twice daily was tried and to the great astonishment of both us and the family a definite relaxing effect could be discerned immediately on the first day. Since then the patient has received Mysoline, except for brief intervals during which other substances, e.g. Meprobamat were substituted. Both the patient and his family maintain, however, that Mysoline is the only effective drug out of those tried. The effect consists in that the patient can more easily carry out voluntary movements and that he speaks better.

Case 2.—A boy aged 10 years suffering from typical athetosis, most pronounced in the left side. Asphyxia for 45 minutes at birth. No icterus. No blood type incompatibility. The patient is tormented by nearly continual involuntary movements. Intelligence normal. Medical treatment hitherto without effect (Parpanit, Amidryl, Peragit, Diamox, Mestinon).

As good effect had been obtained as in the case mentioned above. Mysoline was tried in the same dosage, viz. 125 mg twice daily. Following the first dose which was, by mistake, 250 mg, the boy slept for 15 hours and when his mother woke him the next day and gave him 125 mg, he vomited immediately, fell asleep and slept for 6 hours. The dose was therafter reduced to 25 mg which the patient tolerated well. At present, he receives 50 mg thrice daily.

The effect obtained in this case is, as in Case 1, was better speech and fewer involuntary movements.

The effect of Mysoline consisted of:

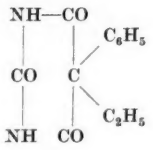
(1) reduction of the increased tone,
(2) better control of the involuntary movements,
(3) improved speech,
(4) a certain soothing effect in some cases.

The only side effect we have observed is drowsiness. In some cases, the children became drowsy without any favourable effect being observed.

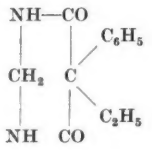
The duration of the effect appears to be for some hours after a dose of 25–50 mg. In some patients, the favourable effect diminished after prolonged use.

It was striking that the tolerance for Mysoline appears to be less in children with cerebral palsy than in other children; the doses employed were 5–10 times less than those used in the treatment of epilepsy.

The formula of Mysoline resembles that of Phenemal to a great extent, as will be seen from this figure.



Phenemal



Mysoline

Butler & Waddel (3) in 1956 found that 5–15 % of Mysoline is converted to and excreted as Phenemal, which only partially explains the effect of Mysoline.

In the following table, the result of Mysoline treatment in 46 cases is recorded. It will be seen that good effect was obtained in 18 out of 21 cases of athetosis and in 14 out of 20 spastic cases. It is, however, our impression that the difference in effect in cases of athetosis and spasticity is much more striking than appears from these figures.

TABLE 1

Effect of Mysoline in cerebral palsy.

Diagnosis	Favourable effect	No effect
Athetosis	18	3
Spastic tetraplegia	11	4
Spastic hemiplegia	2	0
Spastic paraplegia	1	2
Ataxia	1	0
Torsion spasm	1	0
Aphasia	2	1
Total	36	10

Meprobamat

In the same period, Meprobamat was employed in 33 children suffering from cerebral palsy and a favourable effect was found in approximately 50 % as appears from Table 2.

TABLE 2

Effect of Meprobamat in ceberal palsy.

Diagnosis	Favourable effect	No effect
Athetosis	0	7
Spastic tetraplegia	12	4
Spastic paraplegia	2	1
Spastic hemiplegia	3	4
Total	17	16

In some cases, Meprobamat had a pronounced effect on the restlessness and state of tension: such children have managed better in school and

exercises have been facilitated. We emphasize, however, that the effect is less pronounced than that of Mysoline, particularly when children with athetosis are concerned.

Summary

1. Mysoline was employed tentatively in 46 cases of cerebral palsy in dozes of about 5 mg per kg per 24 hours. In cases of athetosis, particularly, a favourable effect was observed in the involuntary movements and the increased muscular tone. The tolerance for Mysoline is less in children with cerebral palsy than in epileptics.

2. Meprobamat was employed in 33 cases of cerebral palsy. A moderately favourable effect was seen in a number of the cases of spastic paralysis but not, however, in cases of athetosis.

La mysoline et le méprobamate dans la paralysie cérébrale.

On essaya la mysoline (5mg/kg toutes les 24 heures) dans 46 cas de paralysie cérébrale. Dans les cas d'athétose en particulier, on remarqua un effet favorable sur les mouvements involontaires et une augmentation du tonus musculaire. La mysoline est mieux tolérée par les épileptiques que par les enfants atteints de paralysie cérébrale. Le méprobamate fut employé dans 33 cas de paralysie cérébrale. On nota un effet médiocrement favorable dans un certain nombre de cas de paralysie spasmodique, mais la drogue fut sans effet pour les cas d'athétose.

Mysolin und Meprobamat in zerebraler Lähmung.

Mysolin wurde versuchsweise bei 46 Fällen von zerebraler Lähmung in Gaben von ungefähr 5 mg kg in 24 Stunden angewendet. Ein günstiger Einfluss auf die unwillkürlichen Bewegungen und den erhöhten Muskeltonus wurde besonders bei Athetose beobachtet. Die Veträglichkeit für Mysolin ist bei Kindern mit zerebraler Lähmung geringer als bei Epileptikern. Meprobamat wurde in 33 Fällen von zerebraler Lähmung zur Anwendung gebracht. Eine mässig günstige Wirkung wurde bei einer Anzahl von Fällen mit spastischer Paralyse beobachtet, aber gar kein Einfluss bei der Athetose.

La misolina y el meprobamato en la parálisis cerebral.

Se ensaya la misolina, en dosis de aprox. 5 mg por kg por 24 horas, en 46 casos de parálisis cerebral. En los casos de atetosis, especialmente, se observan efectos favorables en los movimientos involuntarios y el incremento del tono muscular. Los niños con parálisis cerebral, presentan menos tolerancia la misolina que los epilépticos. El meprobamato fué empleado en 33 casos de parálisis cerebral. Se observaron efectos moderadamente favorables en cierto número de casos de parálisis espástica, mientras que en los casos de atetosis, resultaba sin efecto.

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Aetiology of Non-Diphtheritic Croup

I. Bacteriologic and Serologic Investigation

by LENNART PHILIPSON

MacNab (19) in 1915 was the first to report a case of croup of non-diphtheritic aetiology. He considered haemolytic streptococci to be the causative agent. During the pandemic of influenza in 1918, this syndrome was observed in a high percentage of cases (10, 18). Most investigators believed haemolytic streptococci or staphylococci to be the agents responsible (20, 21). In 1936, Lemierre *et al.* (17) observed for the first time a connexion between septicaemia of Pfeiffer's bacillus and acute oedema of the larynx in children. Alexander in 1940 (1) reported croup due to *Haemophilus influenzae* type B. Sinclair (31) and Rabe (29) corroborated this finding. Rabe reported a supraglottic type of croup in 8 per cent of 347 cases, exclusively caused by *H. infl.* type B. Blood culture was positive in 89.4 per cent of these cases. Neffson (23), however, stressed the varying aetiology of the supraglottic type of croup, but seemed not to have clear-cut indications for the bacteriologic diagnosis of *H. infl.* type B (22).

Attention was called by Beach (5) to an almost identical disease in the chicken caused by a virus, as shown by Burnet & Foley (7). Arden & Duhig (3) concluded from histologic studies and comparison with virus influenzal infections in the chicken and chick embryos that non-diphtheritic croup was in most cases due to a virus, probably related to the influenza viruses. Rabe (28) emphasized in his extensive studies of this clinical syndrome that bacterial aetiology was improbable in most cases of subglottic type. This author refers to these cases as "virus croup", but he was not successful in isolating any virus (30).

Recently, a new type of myxovirus (8) was isolated from cases of non-diphtheritic croup, and a significant rise in antibodies against the agent isolated was shown in some cases. Some serologic connexion with influenza virus A and B has also been demonstrated (26).

A cytopathogenic agent not yet conclusively studied has been found in cases of non-diphtheritic croup by the present author (27), and the results will be presented elsewhere.

The present paper is a study of the role of bacteria in this clinical syndrome. For this reason, a 2½-year series of non-diphtheritic croup was investigated bacteriologically and serologically.

Material and Methods

The series comprises 308 admittances of 232 patients from the Ear, Nose and Throat Department of the University Hospital, Uppsala, during the period January 1954 to August 1956.

The children were referred from the Out-Patient Department with the diagnosis of non-diphtheritic croup. Of the 308 admittances, 269 were investigated bacteriologically and serologically. Since the findings did not differ during the course of 12 months from September to August, the series is presented and evaluated as a whole.

The diagnosis non-diphtheritic croup in this report embraces children with characteristic symptoms such as metallic, hoarse cough, breathing difficulties, and/or inspiratory stridor, and was verified in most cases by indirect laryngoscopy.

The present series, then, comprises various pathologic conditions such as supraglottic laryngitis, subglottic laryngitis, and acute laryngo-tracheo-bronchitis. Of the 308 admittances studied in this report 12 were considered as acute laryngo-tracheo-bronchitis. Confirmation for this diagnosis was either received by bronchoscopic observation or X-ray findings suggesting pneumonic infiltration. In the rest of the cases indirect laryngoscopy when performed revealed a local subglottic swelling. Thus most cases studied would presumably have received the diagnosis subglottic laryngitis, if a differentiation of the diagnosis had been performed. The usual treatment included antibiotics of the tetracycline type, humidificated air, antihistamines and, during the last year of the study, cortisone. Frequency calculations have been made on the number of admittances.

Sampling[1]

Respiratory tract.—As a rule swabs were taken from the nose and throat on admission to the hospital, before antibiotic therapy was administered. After January 1955, nose and throat swabs were taken and analyzed separately. In some cases, several samples were taken during the period of treatment. Nose and throat specimens were also taken on discharge in 55 cases. All swabs were transported within 1 day in slant agar tubes to the Bacteriological laboratory.

Serum.—On admission, 1 to 2 ml of whole blood was taken by finger or heel scalpel cut and the blood collected in U-shaped tubes. A second specimen was taken in the

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[1] The author is indebted to the staff of the Ear, Nose and Throat Department for their kind and painstaking help in taking the bacteriological and serum specimens.

same way between 7 and 14 days later, if travel facilities allowed of a second visit to the hospital.

The capillary tubes were centrifuged and, when the cells were packed, the supernatant serum was pipetted off with capillary pipettes.

Bacteriologic Technique

The following media were used for culture: (1) Ordinary agar plates containing 10 per cent defibrinated horse blood. (2) Ordinary agar plates with 10 per cent defibrinated horse blood and gentian-violet in a final concentration of 1/750,000. (3) Agar containing 10 per cent defibrinated horse blood as haematin (Haematin agar). (4) Agar plates containing 7.5 per cent sodium chloride, 1.0 per cent mannitol, and 0.002 per cent phenol red (Chapman plates, 9). (5) Haematin agar with potassium tellurite in a final concentration of 0.04 per cent. (6) Ascites broth. The ordinary haematin agar plates were incubated in boxes containing about 10 per cent carbon dioxide atmosphere. In the ordinary blood-agar plates, an Oxford strain 209 of *Staph. aur.* was inoculated for satellite phenomena. All plates were incubated at 37°C and read at 24-hour intervals twice. The Chapman plates were also incubated at room temperature for another 72 hours after the 48 hours at 37°C, when they were finally read.

The diagnosis of haemolytic streptococci was based on the appearance of beta-haemolysis on blood-agar plates.

Coagulase tests were performed on all strains of staphylococci isolated from the Chapman plates. Coagulation of rabbit plasma in tubes was the method used. The strains reacting positively to this test were designated as *Staph. aur. pyog.* and the very few negative strains still forming a bright yellow pigment when grown on Chapman plates were diagnosed as *Staph. aur.*

Pneumococci were diagnosed by the optochin test and typed according to Neufeld (24).

Haemophilus influenzae was primarily isolated on haematin agar and current or secondary positive satellite phenomena were considered essential for diagnosis.

Enterococci and coliform organisms were diagnosed according to general methods. No secondary tellurite tests for enterococci or agglutination reactions for pathogenic coliforms were performed.

On analysis of the plates, special consideration was given to haemolytic streptococci, *Staph. aur. pyog.*, pneumococci, *Haemophilus infl.*, enterococci, and coliform organisms. Other species isolated, such as *Staph. alb.*, diphtheroids, *Neisseria pharyngis*, and *Streptococcus viridans* were considered of minor importance.

Serologic Technique

All sera were analyzed for antistaphylolysin (ASta) and antistreptolysin (AST) according to the technique of Packalén & Bergqvist (25) for ASta, and according to Ipsen (13) for AST with the modification for readings used by Packalén & Bergqvist (25). Standard sera from the Department of Biological Standard of the State Serum Institute, Copenhagen, were used for reference.

Some sera were also analyzed for complement-fixing antibodies (AHI) against a soluble antigen of *Haemophilus infl.* according to a method described by Tunevall (34). The first and second specimens from each child were investigated simultaneously to give comparable results. A fourfold increase in titer between the two tests was considered significant.

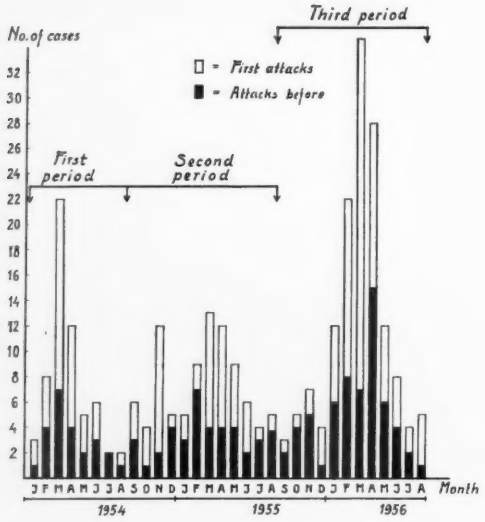

Fig. 1. Monthly frequency of non-diphtheritic croup admitted to the Ear, Nose and Throat Department of the University Hospital, Uppsala.

Laboratory Data

Laboratory data were collected from the case records and the following figures were considered as normal according to Hepler (11) with small modifications: White blood cell count (W.B.C.) 5000 to 10,000 cells/mm^3; micro erythrocyte sedimentation rate (M.S.R.) 0 to 20 mm/hour; total number of eosinophils 0 to 300 cells/mm^3. The W.B.C. and M.S.R. were estimated according to general methods within 24 hours of admission to the hospital. The eosinophils were estimated by multiplying the percentage of these cells in differential cell counts with the total number of white blood cells/mm^3. The differential cell counts were also made within 24 hours of admission.

Rectal body temperature was recorded within 2 to 4 hours of admission and was considered elevated at or above 37.8°C. This figure was based on the studies of Alm (2) and Hesselvik (12) on respiratory infections in children of the age-groups studied.

Results

Incidence of the Disease and Clinical Data

As is seen in Fig. 1, the disease seems to be most common during the months of February to April each year, or at least more children are hospitalized for this disease during those months. In 1956, the number of children hospitalized for this condition exceeded that of the two previous years. The cause of the higher incidence in 1956 is not clear.

The series was divided into the three periods shown in Fig. 1 and at first analyzed separately, but since no differences emerged concerning the factors studied in the present report the results in the following refer to the series as a whole.

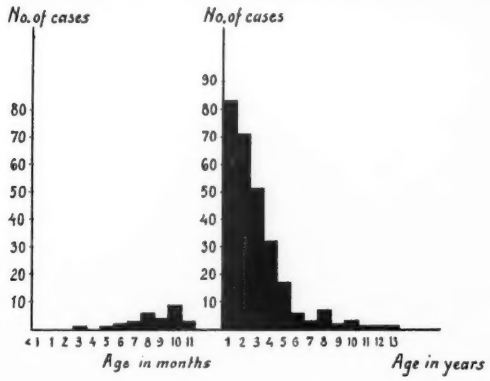

Fig. 2. Age distribution of the author's series.

Fig. 1 shows the extent to which the patients had had the same symptoms earlier. It will be noted that cases with two or more previous attacks were more common in periods of low overall incidence, and that the proportion of initial attacks was higher in high-incidence periods. Recurrences occurred in 40.9 per cent of cases; 24.6 per cent of these patients had suffered two attacks, 7.1 per cent three attacks, and 4.0 per cent four or more attacks during the period of observation. In occasional cases, these symptoms occurred 5 to 8 times yearly. The boy–girl ratio was 2.2:1. Complications were relatively rare. Tracheotomy was performed in 3.3 per cent of the patients. Bronchopneumonia developed in 2.9 per cent of the patients during the period of hospitalization. The total mortality was 1.3 per cent. The fatal cases were all diagnosed as acute laryngo-tracheo-bronchitis at autopsy, and showed in 3 of 4 cases incipient or manifest bronchopneumonia. The average length of hospitalization in the uncomplicated cases was 5.0 days. The case reports yielded data suggesting that only 5.9 per cent of the children had received antibiotic therapy prior to hospitalization.

Age Distribution

The age distribution of the series is shown in Fig. 2. The greater number of the children were under 5 years, and 59.4 per cent below the age of 3 years. The youngest child in the series was only 3 months, and the oldest 13 years.

Bacteriologic Findings

The bacterial species regarded as pathogenic or potentially pathogenic were those usually associated with respiratory infections in children, such as hæmolytic streptococci, pneumococci, *Staph. aur. pyog.*, and *H. infl.* Find-

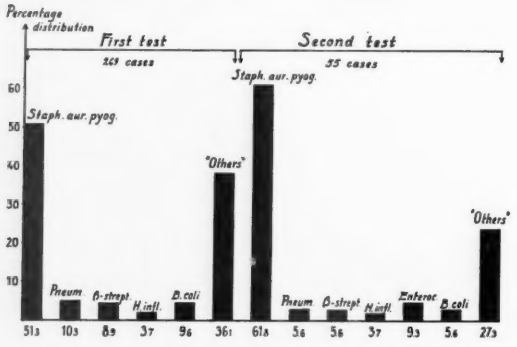

Fig. 3. Results of bacteriological examination on admission (first test) and on discharge (second test).

ings of enterococci and coliforms were also recorded. The presence of these organisms is given in percentage of children examined in Fig. 3. The results of the bacteriologic examination on discharge from the hospital are presented in the same figure.

As is seen in Fig. 3, *Staph. aur. pyog.* was highly prevalent on admission to the hospital, while other bacteria were isolated in frequencies of 3.7 to 10.3 per cent. The group "Others" includes those children in whom bacteriologic specimens showed growth of bacteria considered of minor importance. Pathogens or potential pathogens were absent in nose and throat samples on admission in 36.1 per cent of cases. It may be of interest to note that no haemolytic streptococci were recovered from children below the age of 1 year, and that the incidence of *H. infl.* was extremely low in the age-groups above 5 years. Among the cases considered as acute laryngo-tracheo-bronchitis the pathogens were more common at admittance. Thus, the percentage distribution for haemolytic streptococci, pneumococci and *H. infl.* were in this group 25, 25 and 16 per cent respectively. *C. diphtheriae* was not recovered from any of the patients.

Specimens taken on discharge contained *Staph. aur. pyog.* more frequently than those taken on admission. The incidence of the other bacterial species was about equal on the two occasions. Hospital infection seemed to be chiefly responsible for the haemolytic streptococci on discharge.

Laboratory Data

Body temperature.—Fig. 4 shows that 65 per cent of the children had a rise in temperature to 37.8°C or more on admission.

Microsedimentation rate.—Fig. 4 also shows that 25.2 per cent of the children had a M.S.R. above 20 mm/hour. Of the cases with normal values, 50 per cent had a M.S.R. of 10 to 20 mm.

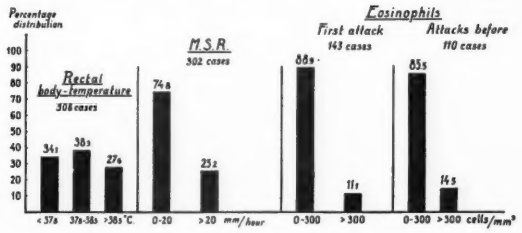

Fig. 4. Rectal body-temperature, M.S.R. and eosinophils in the groups studied.

Eosinophils.—In this analysis, the children having their initial attack and those in whom the same symptoms had occurred on at least one previous occasion were differentiated. There was an increase in eosinophils to values above the limit considered normal in about 10 per cent of both groups, as is seen in Fig. 4.

White blood cell count.—The percentage distribution of leukocytes per cubic millimetre on admission for both the series as a whole, and for children whose specimens showed growth of haemolytic streptococci, pneumococci, or *H. infl.*, is presented in Fig. 5. Of the whole series, 60.7 per cent of patients had apparently normal values falling within the interval 5000 to 10,000 cells/mm³. Only 7.9 per cent were above the 15,000 limit. In the groups in which haemolytic streptococci, pneumococci, or *H. infl.* were isolated from nose and throat specimens, the column representing the last interval above 15,000 cells/mm³ is higher, and in the *H. infl.* group 30 per cent of the children showed values within this interval. Although this group comprised only 10 cases, the recorded counts in two patients were very high, and in one above 30,000 cells/mm³.

Serologic Investigation

The results of the serologic investigation are given in percentage distribution in Fig. 6. This manner of presentation was selected since no significant rise in antibodies was noted between the two tests, with the exception of single cases reported separately below. One hundred and eighty-nine first

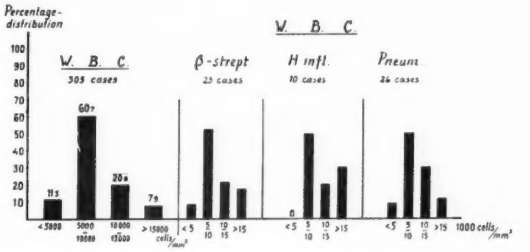

Fig. 5. White blood cell counts in the whole series and in some pathogen carrier groups.

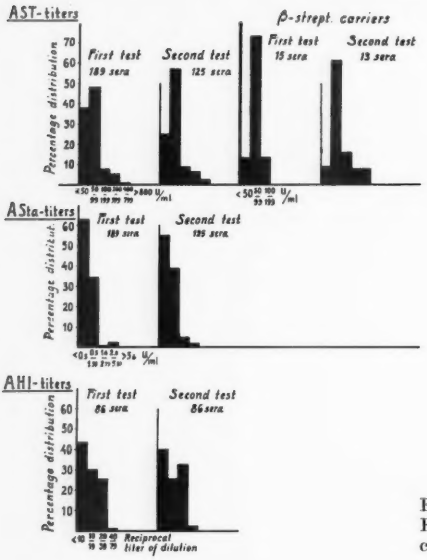

Fig. 6. Results of serological investigation. First test: acute phase-serum. Second test: convalescent serum.

specimens and 125 second specimens of sera were tested for AST and ASta. The AST values of the two tests are given separately in the figure for haemolytic streptococci carriers. In the complement fixation test against *H. infl.*, 86 paired sera were examined.

With the exception of four patients who showed a significant rise, no striking rises in AST were recorded between the two tests. For ASta, only one patient had a fourfold rise in titer. Finally, the complement-fixation test for *H. infl.* gave a fourfold rise in 2 patients. No titer rise in antibodies against *H. infl.* was observed in sera from children below 1 year of age. Owing to lack of sera, the initial dilution in this test was, however, 1/10.

Cases of Bacteriologic Interest

To exemplify the role of some of the potentially pathogenic bacteria isolated in this type of infection, two cases are reported briefly below:

Case 1.—U. A. S. 1855/55 (Fig. 7). Male, 2 years. This infant had suffered attacks on several previous occasions and had once been tracheotomized. He was hospitalized three times during the period of this study for non-diphtheritic croup. His rectal temperature was normal or moderately elevated, but *H. infl.* was isolated from nose or throat on two of the three admissions. The M.S.R. was elevated on admission the second time, but the titers of AST, ASta, and AHI were low during the first and second periods of hospitalization. On admission the third time, the AHI titer was elevated.

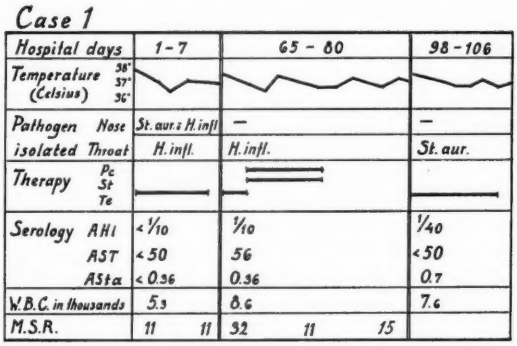

Fig. 7. Croup probably induced by *H. infl.* (For further details see page 272.)

Case 2.—U. A. S. 512/55 (Fig. 8). Male, 1 year. This infant was admitted for the initial attack of non-diphtheritic croup. Marked stridor and breathing difficulties were present on admission. Tracheotomy was performed one day later. A tracheobronchitis developed later and bronchoscopy had to be performed 3 times during 121 days of hospitalization. Some days after tracheotomy, an abundant growth of *Staph. aur. pyog.* was recovered from the trachea. A rise in ASta was noted after the fever period accompanying the positive isolation from the trachea. Despite the persistence in the nose and throat of the *Staph. aur.* strain, the serum titers of ASta fell. A rise in AST was also recorded during the period of observation, the significance of which was obscure.

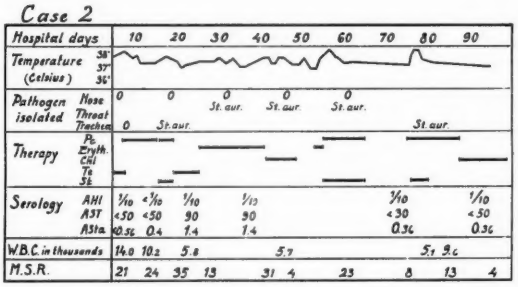

Fig. 8. Probable secondary infection with *Staph. aur.* (For further details see above.)

Discussion

A group of 269 admittances of non-diphtheritic croup were examined for common pathogenic or potentially pathogenic nose and throat bacteria on admission to the hospital, and a smaller group on discharge, during a $2\frac{1}{2}$-year period. The serologic response to three of the pathogens studied, and laboratory data such as W.B.C., M.S.R., eosinophils, and body temperature on admission were also investigated.

The clinical data showed the highest number of admittances during the months February to April each year, the incidence in 1956 being higher than in the other years covered by the investigation.

Fewer complications such as bronchopneumonia, tracheotomy, and death supervened in this than in earlier studies (21, 28).

It must, however, be stressed that the clinical entity non-diphtheritic croup comprises the pathologic conditions subglottic and supraglottic laryngitis, and acute laryngo-tracheo-bronchitis, conditions carrying varying prognosis, frequency of complication, and mortality. Therefore this study, mainly concerned with subglottic laryngitis, may not be comparable with previous series. Further, most studies of this disease were carried out in advance of treatment with antibiotics (23), which may account for the low incidence of complications in this study as compared with others.

Bacteriologic examination showed a high incidence of *Staph. aur. pyog.* both on admission, 51.3 per cent, and on discharge, 61.8 per cent. Other potentially pathogenic bacteria, such as haemolytic streptococci, pneumococci, *H. infl.*, enterococci, and coliforms were not isolated in so high a frequency as staphylococci. With the exception of *Staph. aur. pyog.*, the results show no predominance of any one organism, but the high incidence of the staphylococci on both admission and discharge suggests it to be merely concomitant. Furthermore the same incidence of *Staph. aur.* has been reported in healthy control groups of children in other investigations (16). The absence of any rise in W.B.C. and ASta titers in acute and convalescent sera corroborate the assumption that *Staph. aur.* is not of primary aetiologic importance. In only one case was a fourfold increase in ASta recorded, and in that particular case (Fig. 8) the staphylococci probably gave rise to a complicating infection.

On the other hand, it has been stressed by several authors that the importance of *Staph. aur. pyog.* in clinical infections of the respiratory tract is very difficult to evaluate in the individual case, owing to the low response in ASta in infants (14, 33, 35). It has also been shown (6, 33, 35) that the response in ASta and AST is usually adequate from the age of 1 year. As the present series comprised cases mainly above this age, the ASta and AST response in different age-groups was not differentiated.

Haemophilus influenzae may, as has been shown before (1, 17), be the causative agent in this clinical syndrome, especially in the supraglottic type (4, 29, 31). In the present investigation, the strains were not typed and no blood-cultures were taken, but it seems probable that in at least one case (Fig.7) this agent was of some aetiologic importance. The high W.B.C. values in the *H. infl.* carrier group (Fig. 5) suggest that this agent was involved in a few additional cases. The serologic response has been thoroughly

investigated by Tunevall (6, 33, 35) and, according to this author no antibodies in significant titers were detected in the group below the age of 1 year. Further, a relatively poor serologic response in the age-groups concerned in the present author's series was reported by Tunevall (35). The series was divided into different age-groups as regards AHI, but since no differences were observed above the age of 1 year the results are presented collectively. Nevertheless, there seems to be reason to exclude *H. infl.* as the causative organism in the majority of these cases. This assumption is borne out by the low isolation frequency (3.7 per cent), the normal W.B.C. in 60 per cent of cases, and the significant antibody rise in only 2 cases. It is further corroborated by the low incidence of *H. infl.* type B croup in other investigations (4, 29) and by the fact that this organism has been isolated chiefly from cases of supraglottic type, a clinical condition not generally diagnosed as non-diphtheritic croup at this hospital.

Haemolytic streptococci and pneumococci can probably be ruled out as possible causative agents for the same reasons as the two other species mentioned above. In particular, the incidence of these organisms on admission, pneumococci 10.3 per cent, and haemolytic streptococci 8.9 per cent, appears to conflict with the assumption of any major causative role.

Typing of pneumococci according to Neufeld showed the same types to be present on admission and on discharge, offering further corroboration of the minor importance of pneumococci in the aetiology of the disease.

The generally poor serologic response against streptococci, staphylococci, and *H. infl.* might be due either to the fact that the pathogens studied are not involved as pathogens in this disease, or that the disease—if caused by bacteria— gives a very poor antibody response. The early administration of antibiotics and cortisone might also influence the antibody response, as shown by Ström *et al.* (32) as regards antibiotic. However, the results of the present investigation suggest that common potentially pathogenic bacteria of the respiratory tract were of no major importance in the aetiology of the majority of the cases in the series. In two cases, as mentioned earlier, bacteria may have been involved, probably as the primary agent in one (Fig. 7), and as a secondary complicating agent in one (Fig. 8). The higher isolation frequencies of the pathogens studied in cases with acute laryngotracheo-bronchitis vaguely suggest that bacteria play a more prominent role in the aetiology of this disease. As the presented series includes only 12 cases with this diagnosis no final conclusions could be made.

Our sparse knowledge of the mode of bacterial infection in young children makes it difficult to evaluate the bacteriologic findings. *H. infl.*, haemolytic streptococci and pneumococci are known to play a dominant part as pathogens in the age-groups concerned, and they may also be of some aetiologic

importance in this type of infection, but the author's results afford little or no supporting evidence.

The results of the present study suggest that in the majority of cases non-diphtheritic croup of the subglottic type may be of primary viral causation if an infectious aetiology is accepted: further studies along this line are in progress. On the other hand, the disease might be of bacterial origin in some cases and of viral origin in others, as postulated for enteritis in infancy (15). A constitutional or hereditary factor independent of viruses or bacteria may also be involved as a predisposing factor to croup. An investigation concerning this problem is under preparation.

Summary

A series of 269 admittances of non-diphtheritic croup was studied bacteriologically and serologically. Laboratory data such as white blood cell count, microsedimentation rate, total number of eosinophils, and rectal body temperature were recorded. In 51.3 per cent of the patients *Staphylococcus aureus pyogenes* were isolated on admission. Other pathogenic bacteria such as haemolytic streptococci, pneumococci, and *Haemophilus influenzae* were isolated in frequencies between 3.7 and 10.3 per cent on admission. The majority of the patients had elevated body temperature, a slight rise in microsedimentation rate, and normal counts of white blood cells. The serologic investigation comprising antistaphylolysin, antistreptolysin, and complement-fixing antibodies against *H. infl.* showed a significant rise in antibodies from acute phase to convalescent sera in only a few cases. The aetiologic importance of bacteria is discussed, and a probable viral causation considered.

Etiologie du croup non diphtérique.

I. *Investigation bactériologique et sérologique.*

L'auteur fit une étude bactériologique et sérologique d'une série de 269 individus hospitalisés pour croup non diphtérique. Il rassemblait des données de laboratoire comme la numération leucocytaire, la vitesse de la microsédimentation, le nombre total des éosinophiles et la température du corps. Chez 51,3 % des malades, le staphylocoque doré pyogène fut isolé à l'admission. D'autres bactéries pathogènes, comme les streptocoques hémolytiques, les pneumocoques et l'Hémophilus influenzae, furent isolés dans de 3,7 % à 10,3 % des cas à l'admission. La plupart des malades avaient de la fièvre, une légère augmentation de la vitesse de microsedimentation et des numérations leucocytaires normales. L'investigation sérologique, comprennant l'antistaphylolisine, l'antistreptolysine et les anticorps fixant le complément contre l'Hémophilus influenzae, ne révéla une augmentation importante des anticorps, de la phase aiguë au stade de la convalescence, que dans quelques cas. L'importance étiologique des bactéries et l'existence probable d'un virus responsable font l'objet d'une discussion.

Die Ätiologie des nicht-diphtherischen Croups.

I. *Bakteriologische und serologische Untersuchung.*

Eine Krankenserie von 269 ins Krankenhaus aufgenommenen Fällen von nicht-diphterischem Croup wurde in bakteriologischer und serologischer Hinsicht untersucht.

Laboratoriumsdaten, wie die Leukozytenzahl, Mikrosenkungsgeschwindigkeit, Gesamtzahl der Eosinophilen und Körpertemperatur wurden registriert. Bei 51,3% der Kranken wurde der Staphylococcus pyogenes aureus zur Zeit der Aufnahme isoliert. Andere pathogene Bakterien wie haemolytische Streptokokken, Pneumokokken und Haemophilus influenzae wurden bei von 3,7 bis zu 10,3 Prozenten der Kranken zur Zeit der Spitalsaufnahme isoliert. Die Mehrzahl der Kranken hatte erhöhte Körpertemperatur, eine geringe Steigerung der Mikrosenkungsgeschwindigkeit, aber normale Leukozytenzahl. Serologische Untersuchung auf Antistreptolysin, Antistaphylolysin und komplementbindende Haemophilus influenzae Antikörper brachte nur in wenigen Fällen eine merkliche Steigerung im Antikörpergehalt zwischen der akuten Phase und dem Rekonvaleszentenstadium zutage. Die Bedeutung der Bakterien als ätiologisches Moment wird besprochen und die Möglichkeit von Viren als Urheber in Betracht gezogen.

Etiología del crup no diftérico.
I. *Investigación bacterio-serológica.*

Estudio bacterio-serológico de una serie de 269 casos de crup no diftérico ingresados en el hospital. Se registran los datos de laboratorio, tales como el nivel hemoleucocitario, la producción microsedimentaria, el número total de eosinófilos y la temperatura corporal de los enfermos. Enseguida después del ingreso, se aislan, en 51,3% de los casos, los estafilococos piógenos áureos. También se aislan otras bacterias patógenas, tales como los estreptococos hemolíticos, neumococos y Haemophilus influenzae, en frecuencias variando entre 3,7 y 10,3% al ingresar. La mayoría de los enfermos presentan temperaturas corporales elevadas, un leve aumento de la producción microsedimentaria y niveles hemoleucocitarios normales. La investigación serológica, incluyendo antiestafilolisina, antiestreptolisina y anticuerpos de fijación del complemento contra el Haemophilus influenzae, presentan, en algunos casos solamente, un aumento significativo de los anticuerpos en sueros de fase aguda a convaleciente. Discusión de la importancia etiológica de las bacterias y consideración de la causa viral determinante probable.

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Studies on Osteopetrosis

1. Clinical Report of Three Cases with Genetic Considerations

by H. ENELL and M. PEHRSON

Up to now about 250 cases of this disease have been published, from the mildest forms discovered by chance, to the malignant types starting early in infancy with grave anemia and complications involving the skeleton and the central nervous system.

It is obvious that the disease has a genetic basis. In 1944 Schinz introduced a classification of osteopetrosis from a genetic point of view, and described the following four genetic types:

1. Simple-dominant inheritance with a purely osteo-sclerotic picture; mild course and good prognosis.
2. Simple-dominant inheritance, initially benign, but later a malignant course with serious anemia and a definite interfamilial variability.
3. Simple-recessive inheritance with a mild course and a reasonably good prognosis.
4. Simple-recessive inheritance with early development of a malignant course and a serious prognosis.

The majority of the described cases of osteopetrosis belong to this last group as do the three cases presented here.

Family A 1

Father: Freeholder, born May 22nd, 1910. According to information, healthy. Mother: Born Sept. 22nd, 1911. According to information, healthy.

Case A 1: Brita (the proband), born July 8th, 1949. Two second cousins (Cases A 2:2 and 2:3) suffering from osteopetrosis (the mothers are cousins as are also the fathers). No siblings. Delivery by cesarean section because of placenta praevia. Birth weight 3100 g. The child appeared to be healthy during the first months. At the age of 3 months she showed increasing apathy and pallor while the increase in weight slowed down. At 4 months she was admitted to the Pediatric Department in Boden. She was found to have a bulging forehead and prominent tubera parietalia. The liver was not enlarged but the spleen was palpable below the umbilical level. For blood picture and laboratory

TABLE 1

Development of height, weight and circumference of the head in the 3 cases.

The height is compared with the mean height of Swedish children according to Broman, Dahlberg & Lichtenstein, 1940. The weight is correlated with the mean weight for the corresponding height according to the same authors. The head circumferences are compared to the normal values according to J. Brock (*Biologische Daten für den Kindenarzt*, 1954).

Case	Age months	Height cm	Weight kg	Head circumference cm
A 1	38	93 (− 3)	14.3 (+0.4)	54 (+4.5)
girl born 1949	68	104 (−10)	20.0 (+3.5)	57 (+6.5)
	77	108 (−11)	21.3 (+3.3)	57 (+6.2)
	91	112 (−13)	23.6 (+4.7)	57 (+6.0)
A 2:2	29	82 (−10)	11.8 (+0.4)	51 (+2.3)
girl born 1946	50	91 (−13)	13.7 (+0.5)	54 (+4.0)
	108	110 (−22)	21.5 (+2.7)	56 (+4.6)
	133	118 (−26)	24.6 (+3.2)	57 (+4.6)
A 2:3	15	76 (− 5)	8.2 (−2.5)	52 (+5.5)
boy born 1949	72	100 (−17)	14.3 (−1.3)	56 (+5.5)
	98	106 (−23)	17.1 (−0.6)	58 (+6.0)

N.B.—None of the children are exceptionally fat; high specific gravity.

investigations see table. WR neg. X-rays of the skull, thorax and long bones showed changes characteristic of osteopetrosis.

She was under ambulant control until the age of 3 years and was treated with moderate doses of iron. The motor development was moderately retarded. At 9 months enlargement of the liver was noted. Hemoglobin values varied between 50 and 60 per cent and the color index between 0.8 and 1.0. At the age of one and a half the first signs of weakening vision appeared and somewhat later also nystagmus.

At somewhat more than 3 years of age she was once more admitted mainly because of an asymmetry of the face. Apart from a marked optic atrophy she now displayed the characteristics of a right-sided facial paralysis. The skeletal changes were now more pronounced than before, the long bones were bottle-shaped and showed transverse lines. Serum calcium and serum phosphorus as well as the alkaline phosphatase activity were normal (see Table 3) and the total serum protein level was 7.0 g per 100 ml. A paper electrophoresis of the serum showed a normal pattern. The increasing anemia was treated by means of blood transfusions. Blood group A Rh (+). Since then she has been treated at the Pediatric Department in Boden 23 times mainly to receive blood transfusions. During autumn 1953 ACTH was tried for one month. She has had a fracture of the middle phalanx of the third finger, which healed very slowly. Some calcium balance experiments made during the period 1952–1955 will be published later in Part II.

In March 1957, at the age of 8, she was pale and tired and much less active than other 8-year-olds. Mentally she was hardly retarded. She was rather small for her age but

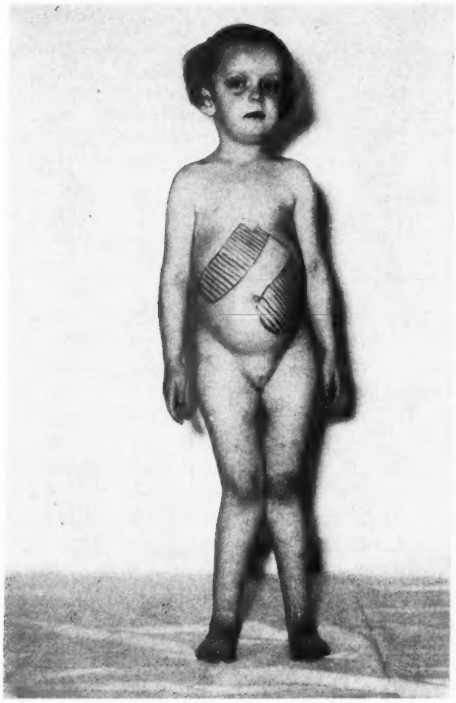

Fig. 1. Photo of case A1, Brita, at the age of 8 years.

within normal limits. Marked genu valga. Dentition was defective, the gums enlarged and puffy, and in the periostium on the left side of the mandible a swelling as large as a plum was observed. A few teeth had broken through but later had fallen out again and only one was left. The spleen was much enlarged and reached below the crista iliaca and medially to the median plane. The liver was palpable 4 cm below the costal margin (see Fig. 1). The optic discs were quite pale, the retinal vessels tortuous and vision was very weak, but her hearing seemed normal. The right-sided facial paralysis had improved somewhat. She had a divergent strabismus and an intermittent nystagmus. For blood picture and laboratory investigations see Table 2. The values for platelets, bleeding time, coagulation time and prothrombin index have been normal. ECG normal.

Diagnosis: Osteopetrosis (+ Anæmia + Atrophia nerv. optici + Retentio dentis + Abscessus gingivae).

Family A2

Father: Road laborer, born August 30th, 1913. According to information, healthy. Mother: Born November 2nd, 1913. Nervous, otherwise healthy.

Case A 2:2. Anne-Marie, born February 21st, 1946. Elder brother and sister healthy, no signs of osteopetrosis. The younger brother, Sverker, has the same disease as the

TABLE 2

Blood picture.

Case	Date	Hemoglobin, %	Red cell count, millions/cmm	Color index	Leucocyte count/cmm	Differential count %					Nucleated RBC /100 leucoc.	Reticulocyte count %
						Myeloblasts	Promyelocytes	Myelocytes	Metamyelocytes	Non-segm. neutr.		
A 1	10.11. 49	68	3.4	1.0	38,000	—	—	1½	—	1	11	
girl	25. 9. 52	45	2.4	0.9	11,000	—	—	5	12	4	27	0
born	15.10. 53	46	2.8	0.8	12,000	2	—	13	7	12	25	0
1949	26. 4. 54	64	3.5	0.9	12,900	—	—	16	11	12	20	34
	14. 6. 54	49	2.8	0.9	14,000	3	—	5	6	21	0	37
	27.10. 54	43	2.4	0.9	16,400	5	—	17	4	27	24	0
	12. 3. 55	46	2.3	1.0	12,500	2	—	21	4	13	34	80
	27. 7. 55	35	1.8	1.0	10,700	4	1	19	9	10	57	0
	21. 2. 56	36	1.8	1.0	9,600	—	—	11	9	15	19	
	12.12. 56	42	2.0	1.0	19,200	7	—	7	6	22	17	8
A 2:2	17. 5. 47	60	2.9	1.0	8,300	—	—	—	—	4	7	4
girl	15. 7. 48	62	3.4	0.9	7,000	—	—	—	—	2	5	0
born	25. 4. 50	43	2.5	0.9	7,000	—	—	—	2	13	7	
1946	27. 3. 52	43	2.4	0.9	17,800	3	—	16	18	6	28	
	9. 2. 55	45	2.6	0.9	6,400	—	—	7	3	3	17	17
	5. 4. 57	37	2.2	0,8	4,900	1	—	8	4	9	28	
A 2:3	9. 4. 49	78	3.4	1.1	16,100	—	—	3	1	8	19	
boy	25. 5. 49	74	3.5	1.1	10,900	5	1	2	1	18		25
born	3. 5. 50	62	3.1	1.0	11,100	—	—	2	1	16	1	
1949	27. 3. 52	62	3.7	0.8	8,700	—	—	—	1½	7½	1½	
	9. 2. 55	48	2.6	0.9	10,900	—	—	5	5	4	26	
	5. 4. 57	43	2.8	0.8	11,800	2	—	12	4	10	10	

patient. The mother took a lot of calcium tablets during earlier pregnancies but took no medicines during the one in question. An X-ray later showed the skeleton of the mother to be normal, as were her serum calcium and serum phosphorus values.

Born normally at term. Birth weight 3700 g. During the first 6 months healthy on the whole. Thereafter troubled by coughs, colds and vomiting. Pale and sallow. She was admitted for the first time to the Pediatric Department in Boden at the age of 15 months. She then had a large head, some anemia, a marked enlargement of the liver and spleen and an insignificant shift to the left in the peripheral blood picture. An X-ray of the skeleton showed a clear osteosclerosis with a thickening of the base of the skull, thickened ribs, compact vertebrae with a cottonreel-like indenture in the ventral contour, clubbing of the metaphyses of the long bones with transverse lines. The optic discs were pale.

In 1947 a fractionized determination of the serum calcium showed a total calcium

TABLE 3

Case	Date	Serum calcium mg/100 cc	Serum phosphorus mg/100 cc	Acid phospha-tases units (Bodansky)	Alk. phospha-tases units (Bodansky)	Total cholesterol mg/100 cc
A 1	4.11. 52	10.1	5.3		7.8	
girl born	8.10. 53	9.8	4.7		7.4	192
1949	26. 4. 54	9.0	3.0		5.7	222
	9. 7. 54	9.0	4.3	6.5	5.2	135
	1.11. 54	9.0	4.7	1.7	5.7	162
	25. 2. 56	9.3	3.6	3.0	6.1	
A 2:2	17. 5. 47	9.5	4.7			
girl born	15. 7. 48	9.0	4.5			
1946	9. 2. 55	9.1	3.6		5.7	120
A 2:3	9. 4. 49	8.2				
boy born 1949	9. 2. 55	9.4	3.5		6.5	240

content of 11 mg % of which 8.6 % was diffusible (Josephson). The amount of calcium in 24 hours' urine was 0.01–0.02 g per day according to several determinations on succeeding days. A biopsy on a rib showed defective resorption and structural alterations, while the original cartilage-bone trabeculae remained, corresponding to the picture in Albers-Schönberg's marble bone (Hultquist).

The anterior fontanel closed at the age of 17 months. The motor development was a little retarded. She began to walk at the age of 18 months, but clumsily, and when 3 years old she still could not run. All the time her head was large and broad between the eyes. The optic discs grew progressively paler and at the age of 6 the right eye was practically blind whereas the left had good vision. She had nystagmus on the right eye. From 5 years onward she suffered from otitis media with frequent relapses causing impaired hearing in both ears in spite of unruptured, pale tympanic membranes. An audiogram in 1955 resembled that in otosclerosis. The development of the ossification centres according to Elgenmark was normal.

She received blood transfusions during her first hospital stay in 1947, after which the hemoglobin values kept between 55 and 75 per cent on iron therapy only, though the white and red blood picture showed an increase in immature forms. Since 1952 blood transfusions have been more and more necessary. She has been treated at the Pediatric Department 8 times altogether. Blood group O Rh (+). For blood picture and laboratory investigations see Tables 2 and 3. The mental development has been normal. She started school at the usual age and has made satisfactory progress. A notable fact is that dentition was fairly normal to begin with but later showed regression. The teeth have fallen out and now she has none left.

In April 1957, at the age of 11 she was in fairly good condition though pale. The spleen is extremely enlarged and reaches the inguinal region on both sides, causing pressure symptoms. Marked genu valga. The optic discs are quite pale. The values for platelets, bleeding time and coagulation time have been within normal limits. Diagnosis: Osteopetrosis (+ Anaemia + Atrophia nerv. optici + Retentio dentis).

Case A 2:3. Sverker: Born February 6th 1949. Brother of Anne-Marie described above. During the latter half of pregnancy the mother took 3 g of calcium daily in tablet form. Birth normal, birth weight 3300 g. He was weak from birth, sucked badly, seemed tired and dull and his hands and feet felt cold. Reached his birth weight at 5 weeks only. Vomited at first and showed a tendency to constipation. At 2 months he was admitted to the Pediatric Department in Boden. The liver and spleen were then somewhat enlarged and there was a slight anemia. The peripheral blood picture showed a slight shift to the left and abundant nucleated red cells. An X-ray of the skeleton revealed general osteosclerosis with a picture typical of osteopetrosis. The optic discs were markedly paler than normal and there were signs of optic atrophy. At about two years of age the anterior fontanel closed. The spleen grew gradually larger. In 1950 it was palpable 4 cm below the costal margin and in 1954 on a level with the umbilical plane.

Anemia increased but patient was sustained on iron therapy until 1954 when blood transfusion became necessary. He was hospitalized 4 times at the Pediatric Department in Boden. Since 1957 the optic discs have been quite white with sharp borders. Vision cannot be determined but seems greatly impaired. The development of the ossification centres according to Elgenmark is normal. Blood group O Rh (+).

Already at the age of 1 year it was found that the boy was mentally retarded with a hydrocephalic triangular shape of the skull. In 1955 his I.Q. was about 40, he could only speak short sentences, was fairly agile, constantly fingering things, and became troublesome. Later he was admitted to a home for mentally defective children. In April 1957 at the age of 8 a check up showed him to be pale, he had pectus carinatum and dentition was retarded. Some of the permanent teeth had fallen out, 5 teeth were left. Liver and spleen were moderately enlarged. For blood picture and laboratory findings see Tables 2 and 3. On April 4th 1952 a biopsy of a rib was made. This was described in more detail by Engfeldt *et al.* in 1954.

Diagnosis: Osteopetrosis (+ Hydrocephalus + Imbecillitas + Atrophia nerv. optici).

The three children described above thus show symptoms indicating the malignant form of osteopetrosis. The diagnosis was established at the age of 4, 15 and 2 months respectively. In the 5 cases published by Hanhart & Schachenmann the diagnosis was made in all of them prior to the age of 5 months; in 2 of them immediately after birth. The diagnosis has also been made before delivery. Thus Jenkinson *et al.* gave an account of a woman who was investigated roentgenologically during the 6th month of pregnancy, and in whom a reasonably typical picture for osteopetrosis of the fetus was seen. The fetus was later stillborn, and was then macerated and hydropic. Cady & Grange described a case of osteopetrosis in an 8-year-old child whose mother had been investigated roentgenologically during the 8th month of pregnancy and the fetal skeleton then showed an abnormally increased density.

As is usually the case the complications involving the central nervous system were in the 3 cases described above facial paralysis, optic atrophy, nystagmus and hydrocephalus.

The roentgenological findings will be discussed in a later article.

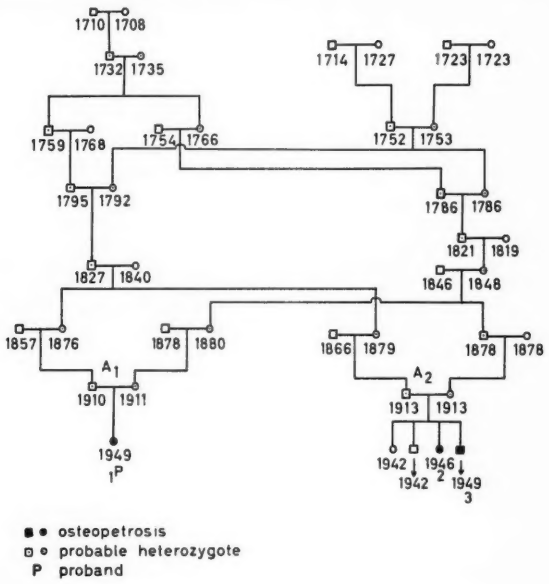

Fig. 2.

Family Investigation

The genealogical studies by other authors, referred to below, describe the majority of osteopetrosis cases as Type 4: Simple-recessive inheritance with early development of a malignant course and a serious prognosis. Seeing that all 3 cases described above seemed, with little variability, to belong to the malignant form of osteopetrosis, the authors have tried to prove the recessive transmission in earlier generations.

Starting with Case A 1:1 of osteopetrosis we have tried to establish as complete a genealogical mapping-out as possible of the patient's family. The family lives in northern Sweden in a coastal district, and the parish records have been carefully preserved. The genealogy of 514 persons was established. The ancestors of the children had for generations lived in the same neighbouring villages. The two families belonged to the same pedigree, showing that the same mutation is reponsible for the disease in both families. (The mothers of the 3 children described were cousins, and the same relationship existed between their fathers.) It was possible to trace the probable heterozygote lines, as seen in pedigree chart (Fig. 2). There are several alternative possibilites.

Our pedigree clearly indicates a simple recessive inheritance, with relationships in the middle of the 18th and 19th century. Apart from the 3

cases known, no secondary cases, either serious or slight, could be found during the genealogical studies. It was also impossible to draw any conclusions concerning the occurrence of other types of hereditary diseases within this pedigree.

Regarding sex distribution no conclusions can be drawn from this material. There are altogether 5 children in the families in question and the two siblings escaping the disease include 1 boy and 1 girl.

In 1948 Hanhart described 2 Swiss families in whom the genealogy could be traced to the earlier part of the 18th century. In each family there were 3 cases of osteopetrosis of the recessively inherited type. In the same work he gave an account of those cases of recessively inherited osteopetrosis which had up to then been described in the literature; it seemed a question of excessive parental consanguinity. In 1950 Cocchi wrote about a Swiss family having osteopetrosis (Type 2), of which only 2 previous families had been described. Including his own cases, Thomson collected a further 7 cases from the literature where osteopetrosis had occurred in successive generations. Drukker established a familial occurrence in 49 out of 121 cases. Hesseling found this disease in a probable uniovular twin where it was likely that the other twin (who died earlier) was also affected by osteopetrosis. Spengler has described the desease in a binovular twin: the other twin was healthy.

Summary

After a short survey of the hereditary predisposition in osteopetrosis, 3 cases of the disease are reported. Two of these occurred in siblings, a girl of 11 and an 8-year-old boy, while the third, a girl of 8 was a second cousin of the former. All suffered from the grave form of the disease with marked changes in the skeleton, abnormal dentition, enlargement of the liver and spleen, grave anemia and optic atrophy. Facial paralysis was present in 1 case. The diagnosis was established at 2, 4 and 15 months of age. The pedigree indicates a simple recessive inheritance. The childrens' mothers are cousins and the same relationship exists between the fathers. Relationships between the families were also traced to the middle of the 18th century.

Etudes sur l'ostéopétrose.
I. *Rapport de trois cas, avec considérations génétiques.*

Après avoir énuméré brièvement les facteurs héréditaires dans l'ostéopétrose, les auteurs en rapportent trois cas. Il s'agit d'une fillette de 11 ans, de son frère de 8 ans, et de leur petite-cousine de 8 ans. Les enfants souffrent de la forme grave de la maladie, avec changements squelettiques prononcés, anomalies de la dentition, hypertrophie du foie et de la rate, anémie grave et atrophie optique. La paralysie faciale est présente dans un cas seulement. Le diagnostic fut établi à l'âge de 2, 4 et 15 mois. L'ascendance indique qu'il s'agit d'un caractère récessif simple. Les mères des enfants sont cousines et le même degré de parenté existe entre les pères. Il fut également établi que les familles étaient parentes au milieu du dix-huitième siècle.

Studien über Osteopetrose.

1. *Klinischer Bericht über drei Fälle mit genetischen Erwägungen.*

Nach einem kurzen Überblick der genetischen Bedingungen bei der Osteopetrose wird über drei Fälle dieser Krankheit berichtet. Zwei dieser Fälle waren Geschwister, ein elfjähriges Mädchen und ein achtjähriger Knabe, während der dritte Fall, ein achtjähriges Mädchen, eine Base zweiten Grades der ersteren Kinder war. Alle litten an der schweren Form der Krankheit mit ausgesprochenen Skelettveränderungen, abnormaler Zahnung, Vergrösserung der Leber und Milz, schwerer Anämie und Sehnervenatrophie. Facialisparalyse fand sich bei einem der Fälle. Die Diagnose wurde im 2. bzw. 4. und 15. Lebensmonat sichergestellt. Der Stammbaum weist auf eine einfache rezessive Vererbung hin. Die Mütter der Kinder sind Kusinen, und derselbe Verwandtschaftsgrad besteht zwischen den Vätern. Eine Verwandtschaft zwischen den beiden Familien wurde auch um die Mitte des achtzehnten Jahrhunderts aufgedeckt.

Estudio de la ósteopetrosis.

1. *Relación clinica de tres casos y consideraciones genéticas.*

Sucinta revisión de las condiciones hereditarias de la ósteopetrosis y descripción de tres casos de enfermedad. Se trata de dos descendientes directos, niña de once años y niño de ocho años de edad y de una tercera niña de ocho años de edad, prima en segundo grado de la antes citada. Los tres pacientes padecen de la forma grave de la enfermedad, con cambios pronunciados del esqueleto, dentición anormal, dilatación del hígado y del bazo, anemia grave y atrofia óptica. Uno de los casos presenta parálisis facial. Al establecerse el diagnóstico, los niños tenían 2, 4 y 15 meses de edad. Los antecedentes familiares indican herencia recesiva simple. Las madres de los niños son primas hermanas y existe el mismo parentesco entre los padres. También ha habido alianzas de familia a mitad del siglo dieciocho.

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Emergence of Primary Vitamin-D Resistant Rickets at Puberty

Genetic Study of Primary Rickets with Familial Disposition

by GUNNAR CHRISTIANSSON

Our knowledge of primary D-vitamin resistant rickets has been extended in recent years. The first complete description of the disease was given by Albright, Butler & Bloomberg in 1937. Subsequently a large number of cases have been reported. Thus Pedersen & McCarroll (1951) were able to diagnose the disease in 25 cases. Comprehensive investigations on the origin of this puzzling condition have also been conducted in Sweden by, among others, Winberg, Bergstrand, Engfeldt & Zetterström (1954, 1955). On the basis of a representative material comprising 13 cases Swoboda recently (1956) detailed the clinical characteristics of the disease.

The symptoms of the disease generally appear in infancy with severe and invalidizing deformations of the skeleton, which often are subjected to surgical therapy but as a rule with only temporary improvement. Most authors point out a tendency to spontaneous healing at the onset of puberty.

Familial occurrence of the disease is not uncommon. Several reports are available in which 2 or more family members are affected. Carlgren (1948) reported the case of a boy who was 4 years old at the last examination (Case 2 below). The diagnosis of primary D-vitamin resistant rickets was established. He also mentioned in passing that the boy's mother suffered from the same condition. In the same family 2 more children were later afflicted with the disease. Since in 1 of these the disease made its first appearance at puberty and in Carlgren's case the condition showed activity despite the onset of puberty, which is contrary to the majority of cases previously described, we were interested to study this family more closely.

Case Reports

Case 1.—G. F., born 1918, mother of Cases 2, 3, 4.

Deformities in the lower extremities at 12 months, which increased in the next few years. Owing to pelvic deformation delivered by cesarian section 1942 (Case 2), 1943 (Case 3), 1947 (Case 4).

When examined in 1957 the patient showed very pronounced deforming changes in both upper and lower extremities. Roentgenologically these changes correspond to those occurring as sequelae of rickets. Patient is short (150 cm). Gait waddling. Blood findings at present normal.

Case 2.—F. F., born 1942, boy (published by Carlgren, 1948).

Cesarian delivery at term, weight at birth 4400 g. Deformities in the lower extremities observed for the first time at 17–18 months of age.

During 1946–50 was repeatedly an inpatient at KLB. On the first admission in 1946, the boy already showed definite clinical, blood-chemical, and roentgenological signs of active rickets. During the hospital periods he received numerous single massive doses of D-vitamin which produced good roentgenological effects upon the rachitic changes. Despite the good results of treatment with almost complete roentgenological healing of the rickets in 1950, the mother refused further therapy for fear of D-vitamin intoxication. The extremital deformities grew worse. Corrective osteotomies on both lower legs were performed in 1953.

Following a check-up of other members of the family the boy was readmitted to KLB at 15 years of age (1957). Puberty had commenced. Stunted growth (133 cm). Pronounced extremital deformities similar to those observed in the mother. Gait waddling.

Laboratory examinations 1957

Blood: Phosphorus 3.5 mg%, calcium 9.7 mg%, alkaline phosphatases 34 Buch & Buch units. Normal values for NPN, cholesterin, bicarbonate, thymol and protein. Normal electrophoresis diagram.

Urine: No proteinuria or glycosuria. Normal sediment. pH about 6.5. Calcium excretion per 24 hours 20 mg%. Chromatographic determination of the amino-acid excretion normal.

Renal function: Amounts of urine normal. Concentration and dilution test of Volhard & Fahr normal. Endogenous creatinine normal value. Clearance of P.A.H. and inulin normal. Intravenous urography normal.

Other examinations: Trypsin test normal. Quantitative determination of fat in feces after administration of fat in excess about 25% fat calculated on dry substance. EEG and ECG normal.

The roentgenological examination of the skeleton showed advanced rachitic changes which had appeared since the examination in 1950, when almost complete roentgenological healing was observed. The roentgen finding together with the results of blood-chemical analysis thus gave evidence of activity in the disease despite the onset of puberty in the boy. This is contrary to the general experience that the condition shows a tendency to spontaneous healing during this period.

Case 3.—E. F., born 1943, girl.

Cesarian delivery at term, weight at birth 4000 g. Breast-fed till 5–6 months. First tooth at 6–7 months. Walked at 13 months. Prophylactic AD-vitamin therapy from

Fig. 1. *Case 2:* F. F., born 1942. A. *Nov. 1946:* Advanced rachitic changes in radius and ulna. Coarsely trabecular loose spongiosa. B. *Nov. 1949:* Calcium-dense zone in the metaphysis after treatment. The rachitic changes unchanged. C. *Oct. 1950:* General decalcification. Loose, coarsely trabecular structure. Increase in breadth of the long bones. Cystic areas in radius and ulna. The epiphysis lines sharp. D. *Jan. 1957:* Advanced rachitic changes in radius and ulna. No treatment 1950–1957.

babyhood. Growth was always retarded and below the lower limit for the normal dispersion. During routine medical examinations no unusual findings in her somatic status were revealed until appearance of the present symptoms. Since her first school

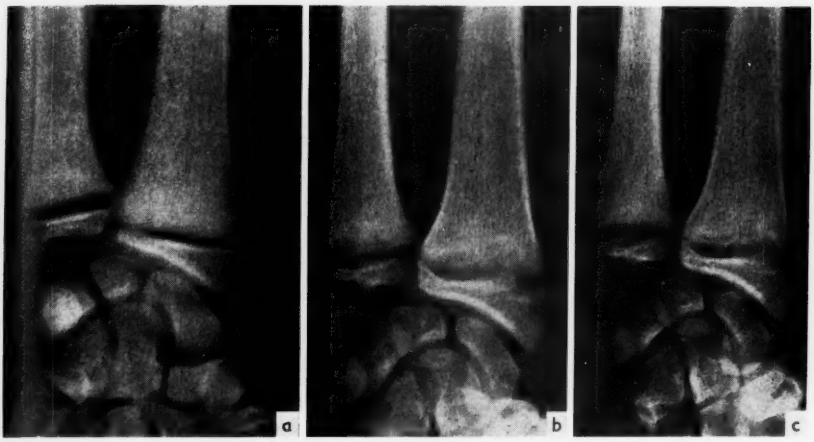


Fig. 2. *Case 3:* E. F., born 1943. A. *Feb. 1956:* Moderately pronounced rachitic changes. B. *June 1956:* Progress of the rachitic changes. C. *Jan. 1957:* Following D-vitamin treatment distinct regression.

year she was much interested in gymnastics and sports and was among the best in some sport activities ("*élite gymnast*"). In recent years she also participated in a voluntary course in ballet dancing.

In the spring of 1955, when she was 12 years old, an incipient slight deformation of the right knee joint was observed. While this deformity rapidly grew worse, symptoms in the left knee also appeared. She had no subjective discomfort in the deformed extremities. At this time the secondary sexual characteristics developed rapidly, and menstruation commenced in the summer of 1956.

The girl was admitted to KLB in May 1956. She was short (139 cm). Puberty had commenced. Extremital deformities with sabre-shaped femurs and genu valgum were clearly observable. The metaphyses in both knee and foot joints showed marked bulging. Gait waddling.

Laboratory examinations 1956

Blood: Phosphorus 3.3 mg%, calcium 9.0 mg%, alkaline phosphatases 28 Buch & Buch units. Normal values for NPN, bilirubin, cholesterin, bicarbonate and protein. Normal electrophoresis diagram.

Urine: No proteinuria or glycosuria. Normal sediment. pH about 6.5. Calcium excretion per 24 hours 5 mg%. Chromatographic determination of amino acids normal.

Renal function: Amounts of urine normal. Concentration and dilution test of Volhard & Fahr normal. Endogenous creatinine normal value. Clearance of P.A.H. and inulin normal. Intravenous urography normal.

Other examinations: Trypsin test normal. Quantitative determination of fat in feces after administration of fat in excess about 22% fat calculated on dry substance.

The X-ray examination in Feb. 1956 showed moderately pronounced rachitic skeletal changes. D-vitamin therapy was at first postponed in view of the commencement of puberty and the therewith connected possibilities of spontaneous healing. Massive

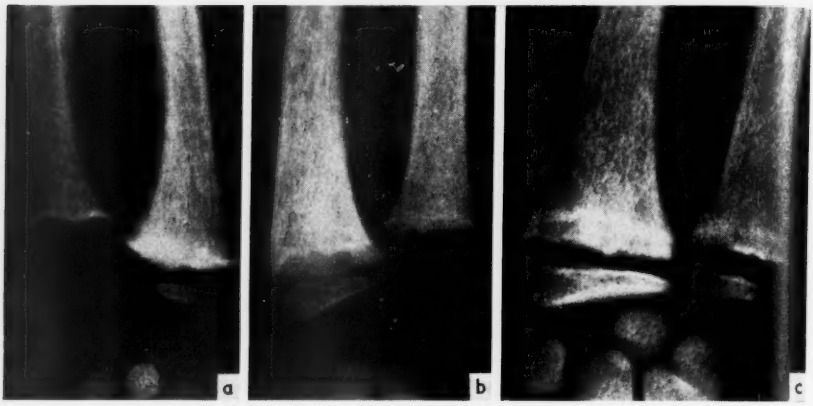


Fig. 3. *Case 4:* M. F., born 1947. A. *June 1948:* Rather advanced rachitic changes. B. *June 1950:* Slight progress with irregular decalcification in the radial metaphyses. C. *Jan. 1956:* Still marked rachitic changes. Small sclerotic zone in the metaphyses following earlier treatment.

doses of D-vitamin were not resorted to until further X-ray examination some months later gave definite proof of rachitic progress. In the course of this therapy we were able to observe a distinct roentgenological regression with simultaneous normalization of the blood-chemical findings.

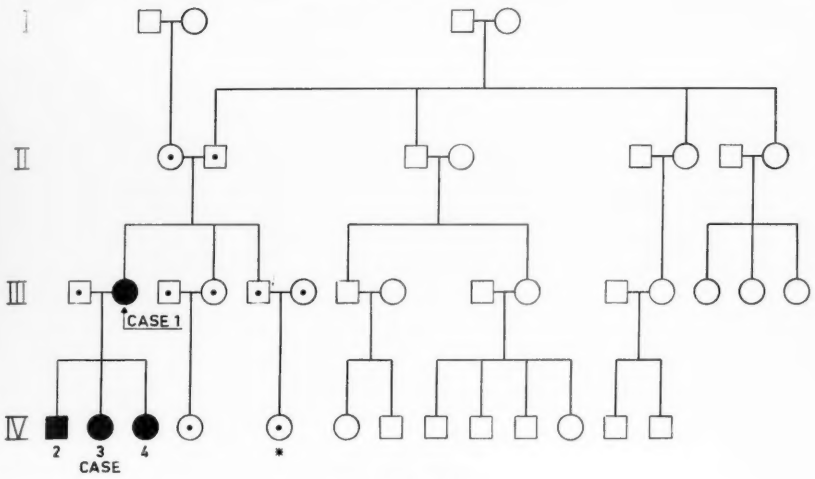
Thus contrary to previously reported cases the disease in this girl first manifested itself after the onset of puberty.

Case 4.—M. F., born 1947, girl.

Cesarian delivery at term, weight at birth 3720 g. At the age of 10 days operated upon for lumbosacral myelomeningocele.

At the age of 1½ years it was possible in this girl also to demonstrate roentgenological skeletal changes of the same character as those observed in the mother and the older siblings. There was blood chemical evidence of rickets in progress. Subsequently the girl has repeatedly been examined clinically at KLB on account of the progressive deforming skeletal changes. The fact that she suffers from total incontinence has made a complete investigation of the etiology of the rickets difficult. Although we cannot wholly exclude a renal cause of the rickets, strong grounds are available for the assumption that in this case, as in the other members of the family, we are dealing with the primary form of rickets resistant to D-vitamin. Sporadic therapeutic trials with massive doses of D-vitamin have been carried out. Owing to the mother's opposition to a systematic treatment we have been unable to assess the amount of vitamin D in order to arrive at a satisfactory judgement of the result of this therapy. During a recent X-ray examination of the skeleton we still observed marked rachitic changes, and the blood-chemical findings indicated activity of the disease.

X-ray examinations of the skeleton have been carried out on 9 other persons belonging to this family line. Except for the cases mentioned, we have failed to find anything unusual in the bone structure. A 6-year-old cousin of the affected children died in 1956 from advanced cystic pancreatic



Genealogical table

□ male

○ female

■ ● examined, affected

⊡ ⊙ examined, not affected, X-ray negative

□ ○ not examined, history negative

* died of cystic pancreatic fibrosis in 1956

Fig. 4.

fibrosis without having shown roentgenological signs of active or healed rickets. No stunting of growth has been observed in members of the family without demonstrable skeletal disease (Fig. 4).

Discussion

We have already mentioned that primary rickets resistant to D-vitamin generally tend to heal spontaneously at the onset of puberty. However, after almost complete roentgenological healing following massive D-vitamin therapy, the disease relapsed in Case 2 after discontinuation of the treatment, and still showed signs of activity both in the blood-chemical and roentgenological findings despite the onset of puberty. Contrary to the other cases, the disease did not become manifest in Case 3, despite unusually severe strain in connection with gymnastics, sports and ballet dancing, until the period of puberty had set in.

The earlier view that rickets and osteomalacia represent completely dif-

ferent disorders is probably not correct in the light of more recent observations. While, according to the current view, rickets is manifested in the growing skeleton, the changes in cases of osteomalacia are found in the fully developed bone. Pedersen & McCarroll have shown that in adult members of families in which rickets resistant to D-vitamin occur, the blood-chemical and roentgenological changes are identical with those found in children afflicted with active rickets. Moreover, in cases observed by these authors, contrary to earlier experience, the condition has shown a clear tendency to progress after the termination of skeletal growth, which indicates that the disease retains its activity even at a relatively advanced age. Although in certain cases the condition shows a tendency to spontaneous healing at puberty, in the light of what has been said and in view of our own experience, strong grounds exist for the desirability of continued therapy even after the termination of puberty, until the blood-chemical findings give evidence of complete clinical healing.

Albright *et al.* (1946) have pointed out that in several cases of primary rickets resistant to D-vitamin, in spite of treatment with massive doses of D-vitamin, the alkaline phosphatase level in serum remained high after terminating the treatment, while other blood analytic data were normal. For such cases these authors have used the designation "chemical osteomalacia with high phosphatase". Undoubtedly the high phosphatase level in these cases is a sign of disease activity, and the treatment should have been more protracted. Like a case of primary osteomalacy mentioned by Elliot (1955), the above reported Case 3 could be successfully treated with D-vitamin in subtoxic doses. However, despite the prolonged treatment, this case showed an elevated alkaline phosphatase level (21 Buch & Buch units), though other blood-chemical and roentgenological findings indicated an incipient healing of the disease.

In all the cases observed by Pedersen & McCarroll, as well as in the majority of earlier published cases, the disease made its first appearance in infancy. The occurrence of clinically manifest symptoms in Case 3 after the onset of puberty is therefore remarkable. Why the condition thus remains latent for years is not clear. The accelerated growth in connection with the attainment of puberty may constitute an explanation of the first appearance of the condition at this juncture. On the other hand, the abnormal stress put upon the skeleton in connection with gymnastics, sports and ballet dancing in this case may conceivably have provoked the clinical symptoms which under more normal conditions would not have become manifest until the process of skeletal growth was terminated. In this case it would have been more proper to designate the disease as osteomalacia rather than as rickets. Thus one should consider the possibility that instances of genetically obscure

osteomalacia occurring in families with rickets resistant to D-vitamin may be cases in which skeletal disease has remained latent since childhood. As in the family investigated here, the condition shows a dominant heredity. An early clinical examination is probably indicated also for symptom-free members of families in which rickets resistant to D-vitamin occur.

The continued observation of Case 3 will show whether a change in the girl's clinical status might occur after the termination of skeletal growth. On the basis of the roentgenological skeletal findings, we may presume that the condition in the mother has indeed healed with very pronounced deforming skeletal changes, but without the residual coarse-meshed spongiosa structure generally found in cases of osteomalacia. Therefore the possibility of complete healing of the rickets is also present in Case 3, despite its strikingly late clinical first appearance.

Summary

An account is given of a family in which the mother and her three children were affected with primary or genuine rickets resistant to D-vitamin. In one of the children the condition first became clinically manifest after the onset of puberty, a course which differs from the majority of previously described cases. The relation between the primary forms of rickets resistant to D-vitamin and osteomalacia is discussed.

Occurrence familiale de rachitisme primaire réfractaire à la vitamine D.

Rapport d'une famille dans laquelle la mère et ses trois enfants furent atteints de rachitisme primaire réfractaire à la vitamine D. Chez l'un des enfants, on ne remarqua aucun symptôme clinique manifeste avant la puberté, ce qui est en contradiction avec le cours de la plupart des cas déjà décrits. Le rapport entre les formes primaires du rachitisme réfractaires à la vitamine D et l'ostéomalacie fait l'objet d'une discussion.

Familiäres Vorkommen von primärer, Vitamin-D-resistenter Rachitis.

Bericht über eine Familie, in welcher die Mutter und ihre drei Kinder von einer primären, auf Vitamin D nicht ansprechenden Rachitis befallen waren. Bei einem der erkrankten Kinder waren die klinischen Symptome nicht vor der Erlangung der Pubertät augenscheinlich geworden, ein Verlauf, der von der Mehrheit der früher beschriebenen Fälle abweicht. Die Beziehungen zwischen primären, auf Vitamin D nicht ansprechenden Rachitisformen und der Osteomalacie werden erörtert.

Manifestación familiar de raquitismo primario, refractario a la vitamina D.

Casuística relativa a una familia, en la que la madre y sus tres hijos padecen raquitismo primario refractario a la vitamina D. En uno de los niños, la condición no ha presentado síntomas clínicos manifiestos hasta alacanzada la pubertad, difiriendo su curso de la mayoría de los casos descritos anteriormente. Discusión de la relación existente entre las formas primarias de raquitismo refractario a la vitamina D y la osteomalacia.

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CASE REPORT

A Case of Agenesis of the Spleen, Congenital Heart Disease and Complete Situs Inversus

by ERIK TERSLEV

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Agenesis of the spleen is a rare anomaly which most frequently occurs in connection with other congenital disorders, primarily congenital heart disease and situs inversus. In his thesis (1955) Ivemark reviewed the cases published till then of agenesis of the spleen and congenital heart disease, and he added 14 new cases. He examined the time relation of development of the spleen and of the heart septa. He demonstrated that the splenic primordia begin to appear (in the fifth embryonic week) at a time when the septa in the atrio-ventricular canal fuse, whereas the division of the cono-truncus region is not terminated until a few days later (Streeter, 1948, quoted by Ivemark). In his series he showed a connection between the anomalies of the cono-truncus region and the a-v region, and concluded that the defective development of the latter might be primary in the reported cases in relation to the cono-truncus anomalies occurring here.

The most recently published cases of agenesis of the spleen, congenital heart disease and situs inversus were reported by Aguilar, Stephens & Crane (1956): three cases which illustrate a characteristic connection between septal defects, abnormal venous return, pulmonary stenosis or atresia, transposition of the great vessels, accessory pulmonary lobes, and partial situs inversus of the abdominal viscera. Further, Levy (1957) published 1 case of agenesis of the spleen, tricuspid atresia, large interatrial and interventricular septal defect, levocardia, a rudimentary right atrium and undeveloped right ventricle, and further pulmonary veins forming a common trunk, opening into the superior vena cava. Most recently, Plowman (1957) published a case with agenesis of the spleen, cor biloculare, right-sided aortic arch and hypoplastic pulmonary artery. Both Levy's and Plowman's cases had a history of severe infection during the course of the disease, as was also seen in 11 out of the 69 cases collected by Ivemark.

A case of agenesis of the spleen, congenital heart disease and complete situs inversus is reported below.

Case record No. 939/57, J. J.—A boy, aged almost 4 months. The only child of healthy parents. The mother had been in good health during the pregnancy, except for a few attacks of tonsillitis. The boy was born 2 weeks before term; weight at birth 2650 g. He was thriving during the first few weeks. At routine examination at 6 weeks signs of congenital heart disease were found, but the patient's condition was so good

then, that admission to hospital was postponed. From that time onwards a tendency to cyanosis on exertion was noticed; it increased in the course of time, and at the age of 4 months he was therefore admitted to Dronning Louises Børnehospital, Copenhagen. On admission the child was a little underweight (height 63 cm, weight 5900 g) with distinct tachypnea at rest and moderate general cyanosis of equal intensity in hands and feet. There were signs and symptoms of congenital heart disease (one common ventricle and, presumably, interatrial septal defect and dextrocardia).

The condition, which was poor on admission, soon aggravated, and the patient died after only 2 days' stay in the department.

Autopsy (Institute of General Pathology, Kommunehospitalet, Copenhagen, autopsy record No. 676/57).—The heart was situated with its apex towards the right. It was almost spherical. When it was opened, only one large ventricular cavity was found (its wall measuring 6 mm in thickness); at the top of which were found two separate ostia, one to the aorta and one to the pulmonary artery. On the left one large atrium was found which communicated with the ventricle through one ostium with 3 valves. A strand of tissue passed across the large atrium from one lateral wall to the other. Two superior caval veins passing from either side of the trachea opened into the atrium. The 4 pulmonary veins combined into a common trunk, which passed caudally and opened either into the lower part of the atrium or into the inferior caval vein. Both lungs had 3 lobes. Complete situs inversus was found in the abdomen with the cecum on the left side, the stomach in the right hypochondrium, and the largest lobe of the liver on the left side. No spleen was present. No signs of universal or localized infection.

Discussion

The reported case was in all probability one of complete situs inversus. The abdominal organs were situated so as to form a mirror image of the normal, and the heart was in the right half of the thorax with its apex pointing towards the right. Excluding the possibility of displacement of the heart to the right owing to pathological conditions in the lungs (not present here), there are two possibilities of explaining the location of the heart: either dextrocardia or incomplete rotation of the heart. In dextrocardia with cyanosis the cause of the latter is often a severe anomaly of the heart (frequently single ventricle); at the same time the occurrence of a left-sided aortic arch is fairly common in these cases, and often there may also be a change in the relation between the aorta and the pulmonary artery (H. B. Taussig). This, compared with the ECG (Fig. 1) typical of situs inversus—in incomplete rotation of the heart the ECG is chiefly normal with positive P and T waves in Lead I—weighs in favor of the view that the case was one of dextrocardia with single ventricle, transposition of the great vessels and left-sided aortic arch, and not one of partial rotation of a heart that was normal originally with regard to position and had a normal left-sided aortic arch (and a single ventricle). Only one case of complete situs inversus combined with agenesis of the spleen and congenital heart disease has been published previously (Gliski 1906, quoted by Putschar & Manion). This is not to be wondered at, since complete situs inversus as a single anomaly is not frequent, and it may be pointed out that this does not *per se* cause agenesis of the spleen, as it is only a mirror image of the normal anatomical conditions.

The case reported here, like that published by Plowman, seems to be an example of the occurrence of an isolated disturbance of the development of the a-v region in the heart (cor biloculare) *without* interference with the division of the cono-truncus

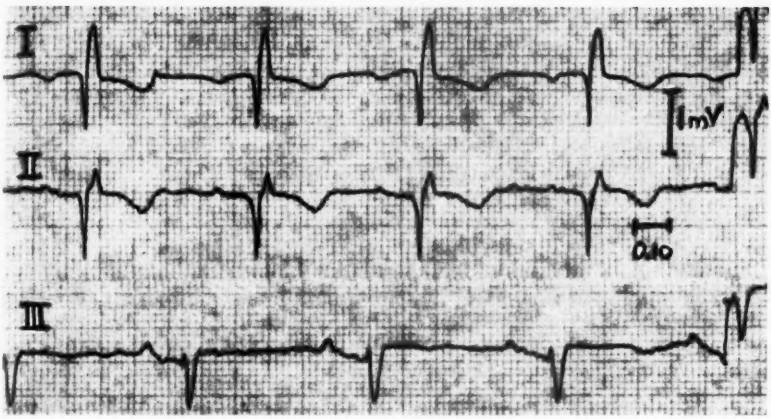

Fig. 1. Electrocardiogram, limb leads: dextrocardia.

region, as the aorta and the pulmonary artery were completely separated, each with its own ostium. Ivemark found in his series (of agenesis of the spleen and congenital heart disease) a simultaneous disturbance of the development of the a–v region and the cono-truncus region in all cases except 2, in which on the other hand no anomalies in either region were present.

The simultaneous development of the spleen and separation of the 2 halves of the a–v region and the 2 parts of the cono-truncus region make it obvious that a noxa affecting the development of one organ has the possibility also of involving the other organ complex. Ivemark considers it probable that a causal connection exists between the development of the a–v region and that of the cono-truncus region, and further that the anomalies of the a–v region are primary in relation to those of the cono-truncus region. The changes in the case reported here suggest that the harmful influences (anoxaemia, toxins or the like), which had caused the developmental disturbances agenesis of the spleen and cor biloculare, did not influence the development of the cono-truncus region. As the complete separation of the aorta and the pulmonary artery is terminated 2 days later than the separation of the 2 halves of the heart (and the splenic primordia are demonstrable simultaneous with the division of the a–v region), it might be thought that the harmful influence had been so scant that it only or chiefly involved the splenic primordia and the a–v region, whereas the cono-truncus region was not involved; if so, because the development of the latter need not be dependent on a normal development of the a–v region (as Ivemark believes).

The autopsy revealed 3 lobes of the lungs on either side, which is a common anomaly in this syndrome. The lobes of the lungs begin to develop synchronously with the spleen and the septa of the heart (Aguilar, Stephens & Crane), and a change often takes place in the direction of the formation of several lobes (Ivemark). In half the cases in Ivemark's series both lungs had 3 lobes.

No details were available about hemorrhage or infection in the mother during the pregnancy, except for a few attacks of tonsillitis. Thus nothing can be said about the cause of the development of the syndrome; this has also been stated in reports of cases previously published.

The diagnosis of asplenia had not been established ante mortem. The presence of situs inversus and the details about the large interatrial and interventricular defects in the heart might possibly have drawn attention to agenesis of the spleen. However, the child's stay in hospital was so short—only 2 days— that it was not possible to undertake the hematologic investigations which might have given the diagnosis. The case was intractable, however, and the recognition of the asplenia would thus not have altered the therapy, which could only be palliative.

Acknowledgements

My thanks are due to Dr. Ib Boesen for good advice during the preparation of the present paper and to Svend Petri, Prosector, M.D., for his kind permission to use the autopsy description of the Institute of General Pathology.

Summary

A case with the syndrome of agenesis of the spleen, congenital heart disease and complete situs inversus is reported. The presence of cor biloculare was ascertained, but the aorta and the pulmonary artery were normally separated, though rotated in relation to each other. The connection between the development of the atrioventricular region and the cono-truncus region is discussed.

Un cas d'agénésie de la rate avec cardiopathie congénitale et situs inversus complet.

L'auteur rapporte un cas de syndrome d'agénésie de la rate, avec cardiopathie congénitale et situs inversus complet. L'existence d'un cœur biloculaire fut démontrée, mais l'aorte et l'artère pulmonaire étaient normalement séparées, bien qu'elles fussent en rotation par rapport l'une à l'autre. Le rapport entre le développement de la région atrioventriculaire et celle du cône et du tronc est, dans le cas étudié, le sujet d'une discussion.

Ein Fall von Milzagenesie, angeborener Herzkrankheit und vollständigem Situs inversus.

Es wird über einen Fall mit dem Syndrom von Milzagenesie, angeborener Herzkrankheit und vollständigem Situs inversus berichtet. Die Anwesenheit eines cor biloculare wurde sichergestellt, aber die Aorta und Arteria pulomonalis waren in normaler Weise getrennt, wenn auch gegeneinander rotiert. Der Zusammenhang zwischen der Entwicklung der atrio-ventrikulären und der Cono-truncus-Gegend in dem vorliegenden Fall wird besprochen.

Un caso de agenesia del bazo, enfermedad cardíaca congénita y completo situs inversum.

Descripción del síndrome de agenesia del bazo, enfermedad cardíaca congénita y situs inversum completo. Se comprueba la existencia de cor biloculare, pero la aorta y arteria pulomonar están separadas normalmente, aunque giradas una en relación con la otra. Discútese la conexión existente en el presente caso, entre el desarrollo de la región atrioventricular y la del cono-truncus.

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Cerebral Lesions in Arthrogryposis Multiplex Congenita

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The pathogenesis of arthrogryposis multiplex congenita (a.m.c.) has been subjected to many conjectures.

One of the views to gain most acceptance has been Sheldon's theory concerning defects of certain muscular groups with secondary sequelae in joints in the form of ankylosis or limited function. One gathers that this view is widely held from the fact that the disease is mentioned, without reservations, as recently as 1956 in the January issue of the *Journal of Chronic Disease* in a general article entitled "Muscular defects" (Warkany). Again, in an introductory survey in a paper published in the *Journal of Bone and Joint Surgery* 1952 (Hillman & Johnson) no other conceivable pathogenic factors are mentioned than those that could properly be included under the heading of "muscular defects".

Nevertheless, Rossi, for instance, has contributed several hypotheses. In Rossi's survey, which embraces 15 points, in addition to better known pathogenic conjectures there are a number of older views: "foetal arthritis", intra-uterine inflammation of the periarticular tissue, oligohydramnios, and others. A number of points are treated in detail with many references to the literature, others are adduced without any stated sources. The latter include conjectures about injury to the central nervous system, and Rossi briefly mentions only 3 of these: "modifications of the nervous system", "foetal poliomyelitis" and "neurotropic virus infections".

Rosenkranz, who must have been one of the first to discuss this disease entity, was able to collect 25 cases of contractures in both the upper and lower extremities. He described the condition as "multiple congenital contractures" and considered the cause to be of neurogenic origin.

Middleton described 7 cases of multiple congenital contractures, among others "club-hand" and "club-foot". He opposed both Rosenkranz' notion of neurogenic origin as well as Sheldon's theory of primary defects in certain muscles. Middleton maintained that dissection failed to confirm these, because the respective muscles, although abnormal, were found to be intact. The same author, however, found fatty degeneration in the affected muscles. He maintained that the condition could be compared with other muscular atrophies with similar pathological findings, and for that reason he coined a new classification for the disease: "myodystrophia foetalis deformans".

Since the thirties, however, several authors have claimed to have found symptoms in a.m.c. referable to the central nervous system (Heijbroek, Herbich, Keizer, Kanof, Aronson & Volk, and Price). Spinal lesions were at first suspected, and many found changes in the spinal cord (Adams, Denny-Brown & Pearson, Brandt, Gilmour, Kuzenok & Rabinovic).

The idea that the origin of a.m.c. is connected with central nervous defects should certainly be seriously considered. Studies of case histories often reveal proofs of C.N.S. involvement. Thus Hagberg, Holmdahl & Söderhjelm describe 15 cases, of which 3 are classified as idiots and one as mental debility. Among the remainder hypothermia is noted in 1 case, strabismus and facial paralysis in another, and strabismus in a third. These patients were not especially examined for cerebral lesions and yet signs of such lesions were commonly encountered.

Lewin reports 2 cases of a.m.c. with deformities of both hands and feet and states that "mentality is much below par".

Three cases are described by Kanof, Aronson & Volk. The authors claim that neurological examinations of these patients indicated involvement of the C.N.S. With support of muscle biopsies and one post-mortem examination it is considered plausible that we are dealing with an infantile form of neuromuscular atrophy rather than a primary disease of either joints or muscles. Of the 3 cases 1 had ptosis and strabismus, and another right-sided facial asymmetry with spasticity in the right arm.

Stern, who coined the now universally accepted name of a.m.c., described 3 cases in his paper besides having seen "several". He considered these children "somewhat backward in their mental development". Mentally backward patients have also been described by Cook, Middleton and others.

Thus many observations support the view that neurological defects are commonly found in cases suffering from a.m.c., and much evidence is available to suggest that these defects are localised in the cerebrum.

The presence of mental defects is opposed by the opinion of Brandt, who, with reference to Ewald, says: "The intellect of these children is unimpaired." Ewald's work, however, only deals with one patient, a young woman, who was found to have normal intelligence.

Rossi, however, who considers that the intelligence is generally unimpaired in cases of a.m.c., characterizes 1 of his 8 patients as mentally retarded. In 1 of the cases he noted a left-sided facial paresis and in 2 he found ptosis palpebrae, a symptom which he considers a common feature in a.m.c.

Müller found among his 8 patients that 2 of 3 adults could earn their own living, and 4 of 5 young patients could attend ordinary schools.

Case Reports

During the years 1953–1956 a series of cases of arthrogryposis have been treated at the Pediatric University Clinic of Lund (Ek), most of them with such striking neurological lesions that the author has been encouraged to make a more detailed investigation of the conditions attendant on this

disease. Examination of these patients has revealed that cerebral changes in a.m.c. are rather the rule than the exception.

The following criteria have been drawn up for the diagnosis. (1) *The disease must be fully manifested already at birth.* (2) *The manifestations must be bilateral and must include both hands and feet!* (3) *The restricted joint mobility must be considerable but not of a special type.* Furthermore, it is considered that additional articular lesions, especially congenital dislocations of the hips, strengthen the diagnosis, although such are not absolutely essential.

These diagnostic conditions do not conform to the opinions of earlier authors, as they are rather more rigorous. The very name of a.m.c. implies that the disease must be fully developed at birth and that the changes of the joints must be multiple.

It is open to discussion, however, if both the upper and the lower extremities must be involved, and if the symmetrical, bilateral characteristics ought to be indispensable.

Authors, who have paid special attention to the symptomatology of a.m.c., include Cook, Mattner, Rocher, Rossi and Stern.

Rocher divided his cases into 3 groups, according to the severity, the extent and the type of the deformities. This division has been criticised by Rossi, who considered it desirable to limit the division to total and abortive forms of the disease. The following quotation from Rossi's summary expresses his own opinion: "This disease usually attacks all the four extremities ... and is always accompanied by serious changes...."

On the whole Mattner shares Rossi's opinion and maintains that there is a "Vollbild" as well as an abortive form of the disease. He does not attempt, however, to define this "Vollbild" in exact terms; instead he reports as a typical example one of his own cases with serious defects in both upper and lower extremities.

In regard to the symptomatology, Stern states that the essential feature appears to be a limitation of movement "in all the joints of the body except the maxillary joint and the vertebral column".

Gilmour contends that "in most cases the disease is generalized in that it affects all the limbs", while Brandt narrows his definition to a "restricted mobility of a number of joints which are fixed in extended or flexed positions".

Other diagnostic definitions appear more irrational, e.g. "a rare but well-defined clinical condition has been described, the characteristic features consisting of one or more joints of the limbs". Later on the same author states that the name of "multiple congenital articular rigidity sums up the leading clinical characteristics of the disease". Another author also defines arthrogryposis multiplex congenita as a "reduced or abolished mobility in one or more joints".

On the basis of the above quotations and the author's personal experience, all the four extremities should be seriously involved symmetrically in order to establish a positive diagnosis. In discussing pathogenicity it is important that the premises should be reliable and that the gliding transition from a.m.c. to various deformities should be eliminated.

Concerning the nature of the immobility of individual joints, Stern states that all

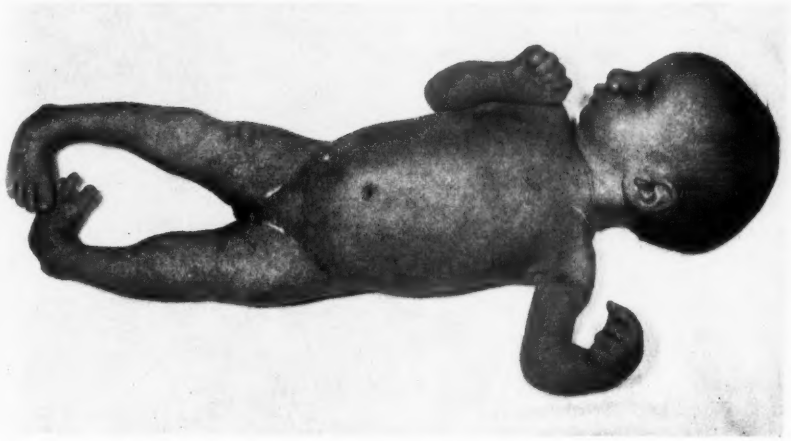

Fig. 1. Case 1. 5 months old. Micrognathia and deformities in all four extremities. Pneumoencephalography: No air in the ventricular system; cavities in cortex, partly in the frontal region, partly in the occipital region on the left side. Ophthalmological examination showed cortical blindness and absence of corneal reflex.

types of movement can generally be demonstrated in affected joints, although their immobility may be variable. No special anomalies of the joints can be proved, as for example in gargoylism or achondroplasia, in which extension defects in the elbow-joints are characteristic. No justification seems to exist for dividing the cases into extension or flexion contractures as Rocher has done.

Stern points out, like several other authors, the fusiform outlines of the affected joints, with strongly thickened, fibrous, periarticular tissue. Concerning the symptomatology and directions for orthopedic interventions, instructive case reports can be obtained in works by Hagberg, Holmdahl and Söderhjelm, Kanof, Aronson & Volk, Mattern, Rossi, and others.

Case 1

E. H., girl born 29.3.1955. No. 15/56. Examination in August 1955. Fig. 1.

The parents and three siblings are healthy. Nothing is known of the family history. The delivery took place prematurely (in a car on way to hospital). Birth weight 2960 g. The patient was cyanotic and convulsive. She had congenital dislocations of hands and feet and micrognathia. She was treated 3 times at the Pediatric Clinic for nutritional disturbances. The patient had repeated severe infections.

The heart was normal on physical examination. The ophthalmological examination showed cortical blindness and absence of corneal reflex.

The state of the joints: Considerable defective development of the mandible was noted. The mouth could scarcely be opened to a width of one cm. Considerable rigidity was present in the arms and the feet. The latter assumed a pronounced equinovarus position. The fingers were rigid with ulnar deviation. No evidence was found of pathological changes in the remaining joints.

X-ray examination: The skullcap presented no change in form or structure. The

Fig. 2. Case 2. 4½ years old. The sister of Case 3. Deformed hands and feet. Kyphoscoliosis. Slight facial asymmetry. No established neurological findings. EEG normal. Pneumo-encephalography normal. I.Q. according to Terman-Merrill 77. Vineland's social maturation scale: social age about 3 years 2 months.

shoulder-joints and the brachia showed no pathological changes. The terminal phalanx of the left thumb was flexed. No pathologic changes were found in the bones of the right and left hand, neither in the thorax, pelvis and hip-joints. Femur and the legs showed no rotation changes. The feet were fixed bilaterally in club-foot position.

Lumbar puncture: CSF contained 3.7 cells/mm³. Nonne and Pandy neg. Bisgaard 1:10.

Electro-encephalography (12 electrodes): A dominant activity of 4–5 c/s. Delta activity was seen during sleep. No focus. EEG normal for the age.

Pneumo-encephalography: The ventricular system contained no air but a considerable amount of air was present in the subarachnoid space. The latter space had an increased width and showed development of fairly large, irregular cavities in the cortex, allocated partly in the frontal region, especially on the right side, and partly in the occipital region on the left side.

Case 2

R.-M. A., girl born 23.4.1952. No. 112/56. Examination in December 1956. Fig. 2. The parents and the family are normal. The only sibling, a sister, has the same disease

(Case 3). The delivery was normal. Since birth she had deformed hands and feet and a pronounced kyphoscoliosis. No established neurological symptoms were observed except a slight facial asymmetry (see Fig. 2). The pupillar, patellar and plantar reflexes were normal. The heart was normal on physical examination. ECG was normal.

The state of the joints: The shoulder-, elbow- and wrist-joints appeared quite normal. The fingers and both hands were maximally flexed. The hands were firmly clenched. The fingers could be forcibly extended into normal functional position, although still deviating ulnarly.

The hip-joints were flexed 90° bilaterally. Rotation could be performed approximately to normal extent. The knee-joints showed no extension defects. The bilateral range of movement was 180°–110°. The shape of the knee was somewhat fusiform. The feet showed a pronounced pes planus and were fixed in a pronounced valgus position. Both the right and the left foot could be flexed 10° dorsally and extended 50°. The spinal column presented scoliosis curving to the left. The gait was very bumpy and wagging.

X-ray examination: A general decalcification of the foot skeleton had taken place without nucleoid changes. A number of narrow concentrated zones in the femur metaphysis were seen. The hand bones showed general but moderate decalcification and a slight widening of the radial metaphysis which contained satisfactory calcium deposition. All the changes described could be equivalent to a healed rachitis.

Electro-encephalography (16 electrodes): A postcentral basal activity of about 7 c/s was registered without any lateral differences. No paroxysmal or focal changes. EEG was normal.

Pneumo-encephalography: No dilatation of the ventricle system was noted, nor any dislocation. The air on the surface and in the cisterns showed no pathological changes.

The general impression of the patient disclosed slightly impaired intellectual functions. During the tests special attention was paid to the patient's motorial disturbances. I.Q., according to Terman-Merrill, 77. Vineland's social maturation scale: social age about 3 years and 2 months.

Case 3

G. A., girl born 18.1.1955. No. 7/56. Examination in January 1956. Fig. 3.

The patient is the only sibling of Case 2. The delivery was normal. Birth weight 2850 g. Since birth the patient has bilateral hand and foot defects. Food intake was very difficult.

The heart sounds were normal. ECG was normal. At ophthalmological examination ptosis was noted in the right eye, and facial paralysis was suspected on the left side (see Fig. 3).

The state of the joints: The fingers of the left hand were deformed in such a way that they were constantly clasped and could not be straightened out. On the right hand the second and third fingers were clasped in the same way and could not be extended. The left shoulder-joint showed a moderate limitation of movement. The left elbow-joint showed an extension defect of 20°, the right elbow-joint showed a somewhat less pronounced defect, the knee-joints were pronouncedly rigid with inconsiderable passive movements bilaterally. The feet were fixed in a valgus position.

X-ray examination: No deformities except external ones could be detected in the bones of the hands and feet. The right hip showed a complete dislocation, and it is questionable if the left hip did not show the same malformation as well. The cranium

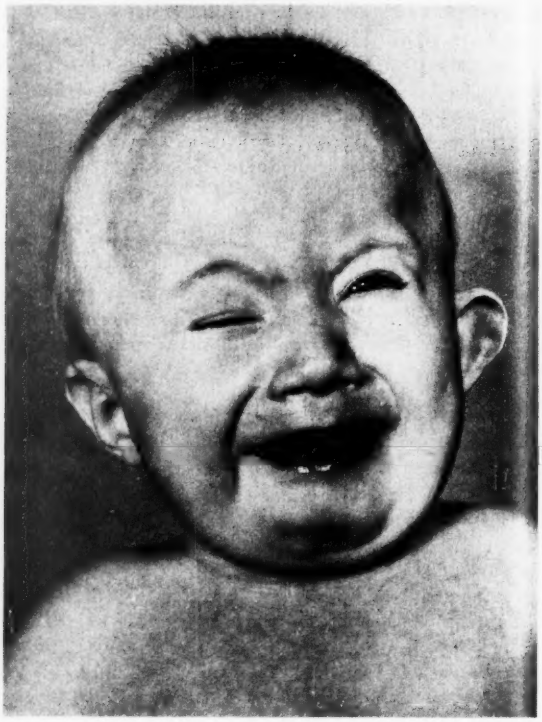

Fig. 3. Case 3. 1 year. The sister of Case 2. Deformed hands and feet. Complete dislocation of the right hip. Ptosis in the right eye, suspected facial paralysis on the left side. Pneumo-encephalography: Wide sulci and large defects in the brain substance.

was somewhat abridged. The sutures had an ordinary width. Sella turcica was normal. No intracranial calcifications or osseus defects were seen.

Lumbar puncture: 0.9 cells/mm³. Nonne neg. Pandy slightly pos. Bisgaard 1:10. WR neg. in the CSF.

Electro-encephalography: A dominant activity of 4–6 c/s was noted without any positive proof of a lateral difference. EEG was normal for the age.

Cisternal pneumo-encephalography: No dislocation or dilatation of the ventricle system was observed. The air accumulated to a great extent on the surface of the hemispheres. The sulci were wide and there were large defects in the brain substance. Porencephaly was present.

Case 4

B. S., girl born 1.10 1943. No. 632/56. Examination in May 1956.

The father is being treated at the Neurological Policlinic with the diagnosis of tardy epilepsy. The child has deformities since birth. She has been repeatedly treated and operated on at an institute for disabled persons. On account of her low I.Q. she was transferred to a shool for mental defectives. I.Q. 43 according to Terman-Merrill.

She appeared in general good condition although thin and delicate. The heart was normal on physical examination. ECG was normal. The Achilles reflex was not pro-

duced. The other spinal reflexes were difficult to assess. The Babinski reflex was negative on the right side, doubtful on the left side.

The state of the joints: The mandibular joints appeared normal, likewise shoulder- and elbow-joints and the spinal column. The hands were slightly displaced anteriorly and fixed in an extreme volar flexion. The hip- and knee-joints were fixed in a slight flexion. The feet presented a slight drop-foot position with fixed pronation.

Lumbar puncture: No pathologic findings.

Electro-encephalography: Normal.

Pneumo-encephalography: The air passed without hindrance into the fourth ventricle, the aqueduct and the third ventricle, which were situated in the medial line and had a normal appearance. Further the air passed into the left lateral ventricle, which had a normal appearance. Despite repeated attempts only small amounts of air entered the right lateral ventricle, on account of which this could not be delineated. Nevertheless, no lateral dislocation of the lateral ventricles could be made out. The left anterior horn appeared normal. A considerable amount of air passed over the surface of the brain. No signs of atrophy were present.

Case 5

R. O., boy born 18.6.1955. No. 1032/55. Examination in October 1955. Fig. 4.

Nothing is known of the family history. The boy had no sibling. The delivery was normal. Birth weight 2030 g. The patient was born with deformed hands and feet.

The heart showed normal findings. ECG elicited no comments. A left inguinal hernia was noted.

The state of the joints: The hands were constantly clasped and could scarcely be extended. The feet were laterally dislocated. The hip-joints were rigid with considerable bilateral extension defects. The lower jaw was retracted and the mouth could not be completely opened.

X-ray examination: The hip-joints presented a bilateral dislocation. The form and position of both feet indicated considerable pathological changes. Calcaneae were fixed to the metatarsi at an angle of 45°, which were dislocated proximally and backward. The thumbs on both hands were short. Apart from these findings no malformations could be registered. The cranium was normal.

Since birth the patient had difficulties with food intake, and he often had infections with high temperature. After a long, constantly febrile period with enterocolitis, the patient died in Jan. 1956.

Post-mortem diagnosis: arthrogryposis multiplex + congenital dislocation of the hips + pronounced atrophic musculature within the extremities + papillary necrosis in the kidneys + multiple bronchial pneumonias. Histologically the heart appeared normal. The C.N.S. was not examined.

Case 6

S. B., boy born 11.9.1952. No. 27/53. Examination in January 1953.

Nothing is known of the family history. Birth weight 3450 g. Since birth he had deformed hands and feet and bilateral inguinal hernia.

The state of the joints: On the left hand the second and fifth fingers were deviating ulnarly about 30° in the metacarpophalangeal joints, which had an extension defect of 70°. The first interphalangeal joints showed a slight hyperextension. The fingers of the right hand were deviating ulnarly and the hand was clasped. There was a radial

Fig. 4. Case 5. 5 months old. No siblings. Birth weight 2030 g. Deformed hands and feet, left inguinal hernia. Congenital dislocation of the hips bilaterally. Died of enterocolitis before futher clinical investigation could be made.

deviation of the terminal phalanx of the third finger. The left foot was kept in a varus position of about 100° and was adduced 90°. The right foot was still more adduced in a similar varus position. The rest of the joints showed no pathologic changes.

X-ray examination: The bones of the feet showed extreme bilateral pes equinovarus. No definite lesions were found in the hip-joints.

The patient was admitted to the Pediatric Clinic because of rhinopharyngitis. He was treated with streptomycin and became free from infectious symptoms, but his temperature continued to show extreme fluctuations. The greatly increased tone in the patient's abdominal musculature kept the head constantly bent backward. He appeared markedly underdeveloped, was unable to coordinate his eyes, or to balance his head. The patient's cerebral affection could not be further investigated because of his deteriorated conditions. The heart was normal.

Lumbar puncture: The cerebrospinal fluid was assessed as pathologic.

After a quick rise in temperature to 41.7°C, the patient suddenly died. Necropsy was refused by the parents.

Case 7

L. A., girl born 7.10.1949. No. 1055/56. Examination in May 1956. Fig. 5.

The parents and two siblings aged 9 and 12 are healthy. A sister few months old died at home in 1945. Earlier she had been treated in the same clinic with the diagnosis of cerebral lesions. She had symmetrical contractures in hands and feet.

This patient has had deformed arms and legs since birth. Birth weight 3500 g. She has been repeatedly treated in various hospitals.

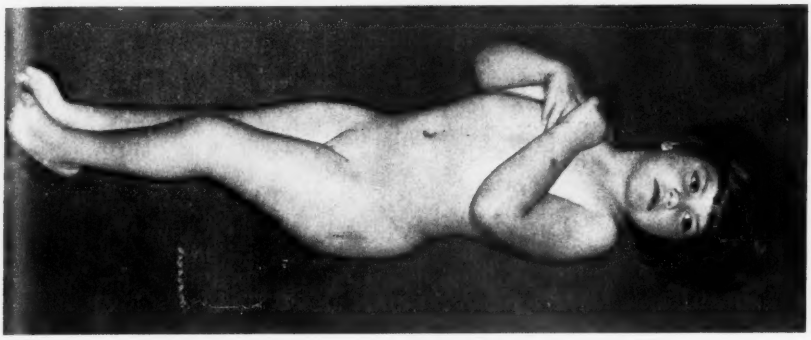

Fig. 5. Case 7. 6½ years old. A sister died with a somewhat similar disease. Very restricted movements in the majority of the joints. Congenital bilateral dislocation of the hips. Mentally very retarded. Pneumo-encephalography: Air filled a medial cavity of finger-tip size in the posterior fossa. An increased width of the sulci in both the anterior convexity of the frontal region and the middle and posterior parietal region.

The heart sounds were normal. ECG was normal. Ophthalmological examination revealed a normal ocular state. Both the position and the movements of the eyes were well coordinated. The biceps, triceps and patellar reflexes were elicited and failed to reveal positive proof of any lateral difference or increased deviation. Neither the plantar reflexes nor Babinski could be elicited. The cranial nerves were normal. There was no nystagmus. Accommodation was normal. The corneal and pupillary reflexes were normal.

The state of the joints: The movements of the head and the mandibular joints were normal. The motions of the shoulder-, elbow- and wrist-joints were greatly limited. The fingers were rigidly outstretched, making it difficult for the patient to clasp anything. Scarcely any movement occurred in the hip- or knee-joints. The feet were markedly deformed.

X-ray examination: No change in the form or the structure of the cranium was present. The mandibular joints were normal. The lower part of the spinal column revealed a slight scoliotic curvature to the left, but no other pathologic changes were seen in the joints or the skeleton. A moderate, general decalcification existed in both shoulder-joints and elbow-joints, without any further pathologic changes in these joints or this part of the skeleton.

The third, fourth and fifth fingers on the right hand were deviating volarly. Moreover, the fifth finger was flexed radially. The second finger differed from the rest only by the absence of ulnar deviation. No pathologic changes were seen in the skeleton or the joints. The same findings were registered in the bones of the left hand, although the bending of the fifth finger was much more pronounced. A bilateral dislocation of the hip-joints was present. The head of the femur articulated on both sides with ischium about two fingers' breadth above the acetabulum. The pelvis displayed an elongated deformation. The right half of pelvis was smaller than the left half. The right and the left knee-joints showed periarticular decalcification. On the right side there was an inclosed space between the femur and tibia with a laterally open angle. The bones of the right and the left foot showed a pronounced, general decalcification, without any pathologic changes in the bones or the joints.

Fig. 6. Case 8. 2½ months old. No siblings. Micrognathia. Limited movements in most joints. Pneumo-encephalography: Abundant amount of air covering the surface of the brain in partly greatly dilated sulci. Cortical atrophy.

Lumbar puncture: Normal findings.

Electro-encephalography (13 electrodes): An unpatterned curve without perceptible alpha waves. No focal findings. Variations within normal range.

Pneumo-encephalography: The air passed freely into the cerebral ventricles which failed to show any dilatations or dislocations. The posterior fossa displayed in the medial cavity an air-filled space of finger-tip size. There was increased width of the sulci in both the anterior convexity of the frontal and the middle and posterior parietal regions.

The patient was in such low mental state that Terman-Merrill or similar tests could not be performed satisfactorily. She uttered occasional, indistinct words.

Case 8

K. S., girl, born 30.9.1956. No. 1162/56. Examination in December 1956. Fig. 6.

The parents are healthy. No similar case known in the family history. No siblings. The delivery was normal. Birth weight 2550 g. The food intake was difficult during the first weeks.

On physical examination the heart was normal. ECG was normal.

The state of the joints: The upper and lower extremities were greatly dislocated. The shoulder- and the hip-joints displayed very limited motion. The elbow- and knee-joints presented extension defects. The hands were fixed in an anteriorly dislocated position. The feet showed equinovarus positions. The patient had a remarkably small chin.

X-ray examination: The bones of the right and left hand and foot were normally developed for the age as regards nuclei, but the foot-joints showed an equinovarus

position. A longish, periosteal thickening existed along the whole left humerus. The change might possibly be due to a periosteal reaction after a haemorrhage.

Electro-encephalography: Normal.

Pneumo-encephalography: An abundant amount of air covered the surface of the brain in partly greatly dilated sulci. The changes in the upper part of the parietal region on the right side were most pronounced. Cortical atrophy was present.

Discussion

Among the eight cases presented, four (Nos. 1, 3, 7 and 8) showed definite, objective signs of organic cerebral lesions. It is probable that some form of serious cerebral defect also is present in Case 4. This imbecile patient never showed air-insufflation of the right lateral ventricle, in spite of repeated attempts, and her pneumo-encephalography was therefore interpreted as very suspect.

Case 2 showed normal pneumo-encephalography. She had a slight facial asymmetry but no definite neurological findings. Her intelligence was obviously low. Thus no positive proofs of a cerebral injury could be imputed, even though the case may be regarded as suspect.

Cases 5 and 6, in whom no or insignificant symptoms, indicating a cerebral involvement, could be found, were also the least investigated ones. The author had not seen these patients in person.

Neither EEG nor pneumo-encephalography was done here. Unfortunately the C.N.S. was not examined at the necropsy of Case 5, and in Case 6 a post-mortem was refused. However, it can be pointed out that Case 6 showed signs of cerebral injury (mental backwardness, rigidity and hyperpyrexia).

It is remarkable to find two siblings (the parents were second cousins) in the material. Besides, the patient L. A. had a sister with a similar disease.

Some authors (Middleton, Gilmour) refuse to admit that a.m.c. may be established by hereditary factors. In many case reports relationship between the parents is denied. A. m. c. in one twin has been described by Hillman & Johnson and in uniovular twins by Heijbroek. Familiar cases have also been reported by Rossi, Ruiz Moreno & Geser. Rossi states that "the condition is probably hereditary in analogy to other multiple congenital deformities". He refers to works by Fraser Roberts and Heijbroek.

The hereditary, multiple deformities in sheep, described by Fraser Roberts, are of interest in this connection. "The most striking feature of the condition is that the lambs are born with some or all the limbs rigidly fixed with only a small degree of movement possible of the joints." According to Fraser Roberts "a homozygous state of an autosomal recessive factor" was concerned.

In none of the eight cases in this material do we find complications during pregnancies mentioned. Some of the cases were born prematurely and some had remarkably low birth weights. Unfortunately it cannot be said that these patients have been sufficiently examined in this respect, since only two of the mothers have been personally consulted, and no obstetric journals have been examined. In the literature, however, records are often encountered that verify abnormal conditions during the pregnancies or at parturition (Earling, Gilmour, Kanof, Aronson & Volk, Mattner, Middleton, Price, Rocher, Schulte, Schulz, Sheldon).

Among our 8 cases ECG was taken in six, and in no case were pathologic findings recorded. In all, the auscultatory conditions were normal. The necropsy finding in patient No. 5 showed nothing remarkable concerning the heart.

These results agree with the reports in literature, where congenital heart disease or other anomalies are seldom described in patients suffering from a.m.c. (Gilmour). Thus symptoms indicating any form of systemic disease seldom are found in the often very detailed case reports (Hagberg, Holmdahl & Söderhjelm, Kanof, Aronson & Volk, Mattner, Middleton, Müller, Rossi, Schulz and others).

X-ray examinations of the skeleton showed no general changes among the author's patients, with the possible exception of sporadic signs of osteoporosis. Such observations are confirmed by other case histories (Brandt, Ealing, Hagberg, Holmdahl & Söderhjelm, Mattner, Rossi, Schulte, Sheldon).

The neurological symptoms described in a.m.c. can generally be assigned to the field of the cranial nerves. Thus these patients often show a ptosis palpebrae or a facial paresis (Rossi). Disturbances of tonus or the disappearance of reflexes may occur (Kanof, Aronson & Volk). No reflex anomalies have been definitely proved among the author's own cases, a finding that agrees with most reports in literature (Brandt, Middleton, Stern).

Apart from rare cases with multiple malformations in entirely separate organs it would appear from literature that patients with a.m.c. do not generally display symptoms other than those which may be considered secondary to the C.N.S. lesions.

A number of extremely abnormal children, mostly in connection with the so-called pterygium syndrome, may have symptoms from the muscles and joints that justify the diagnosis of a.m.c. (Mattner, Rossi & Caflisch, Ulrich). In the majority of those cases, however, signs of cerebral lesions are also present. Thus in these patients the deformities of the extremities may possibly be considered secondary to neurogenic causes. For a closer study of the problems in connection with the pterygium syndrome, and its possible

relationship to a.m.c., works by the above-mentioned authors can be recommended.

Any discussion about the concise nature of the hypothetical injury to the C.N.S. is beyond the scope of this work. It is the author's contention that many factors speak in favour of a foetal defect in the C.N.S. It is at present impossible to fix the time of its occurrence. But owing to the selectivity of the type of the hypothetical defect it would seem reasonable that it takes place at the end of or after the organo-genetic period.

Summary

The author reviews sundry earlier conjectures about the etiology of arthrogryposis multiplex congenita (a.m.c.).

Eight cases are described. In four of these the author demonstrates established findings of organic cerebral lesions. A fifth case, an imbecile girl, is a suspected case on the basis of findings with pneumo-encephalography. Of the remaining three cases two arouse suspicion of similar lesions, whereas the third and least investigated case leaves the question unanswered.

As judged by these cases it would appear that cerebral injuries are commonly encountered in patients suffering from a.m.c. This statement, which has not before been mentioned, is also supported by a critical examination of earlier case histories, in which symptoms indicating cerebral lesions were often found.

It is important that the diagnostic criteria in a.m.c. should be fully satisfied. A brief review is given of opinions expressed by other authors about the symptomatology in a.m.c. Finally it is maintained that the dominant symptomatologic conditions in a.m.c. seem to be the pronounced, bilateral deformities present at birth in both the upper and the lower extremities.

Lésions cérébrales dans des cas d'arthrogryposis multiplex congenita.

L'auteur donne un aperçu sommaire de conjectures antérieures concernant l'étiologie de l'arthrogryposis multiplex congenita. Il rapporte 8 cas traités par lui-même. Dans 5 d'entre eux, l'auteur trouve des signes établis de lésions cérébrales. Parmi les trois cas restants, deux d'entre eux ont réveillé des soupçons d'avoir de telles lésions, tandis que le troisième cas a laissé la question sans réponse.

Hirnbeschädigungen bei Arthrogryposis multiplex congenita.

Verfasser gibt zunächst eine kurze Zusammenstellung der die Aetiologie der Arthrogryposis multiplex congenita betreffenden, früher ausgesprochenen Hypothesen. Acht eigene Fälle werden präsentiert. Bei fünf unter diesen wurden Zeichen von zweifelloser Hirnschädigung festgestellt. Unter den drei restlichen Fällen befanden sich zwei mit verdächtigten Hirnläsionen, während bei dem dritten diese Frage offen gelassen werden musste.

Lesiones cerebrales en la artrogryposis múltiplex congénita.

El autor resume brevemente conjeturas anteriores acerca de la etiología de la artrogryposis múltiplex congénita. Casuística de ocho pacientes particulares. En cinco

de estos casos el autor halla síntomas establecidos de lesiones cerebrales. En los demás tres casos, dos de ellos hacen nacer sospechas en cuanto a tales lesiones, mientras que el tercer caso deja el problema sin resolver.

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A. Drablös: **A case of chronic hypervitaminosis A.**

A case of chronic vitamin A intoxication in a 7-month-old boy is described. The symptoms were apparent after 100 days' administration of approximately 80,000 U of water-soluble vitamin A daily. In addition to the usual, by now well-known, symptoms of anorexia, failure to thrive, skin manifestations, painful swellings over the bones in the extremities and the characteristic X-ray finding of cortical hyperostoses, this patient was found to have a transitory hydrocephalus with marked craniotabes.

Martin Seip and Richard Amlie: **New principles in infant nutrition.**

On the basis of studies undertaken at the Paediatric Department, University of Oslo, infant nutrition, as it is practised in Norway, has been submitted to a new evaluation. The investigations indicate that the Norwegian infant's diet is poor in iron, and that it could benefit from a higher calcium, and to a certain extent also vitamin B, content. It seems to be adequate in other foodstuffs, vitamins and minerals. It has been shown that even in a full-term infant one cannot expect the stored iron to be adequate after the fourth month. From that age onwards the infant should receive foodstuffs rich in iron. The iron intake recommended by the Food and Nutrition Board of the National Research Council, that is to say, 6 mg per day, is, in the opinion of the authors, in many cases not sufficient to prevent an iron deficiency. They recommend therefore a daily iron intake of 10–15 mg after the age of 4 to 5 months. The iron content of the diet should be increased by giving infants more meat, liver and vegetables. In addition one should prefer baby cereals fortified with adequate amounts of iron, calcium and B vitamins. Solid foods should be started before the age of 4 months. (Published in *Tidskr. for den Norske Lægeforening*, 77, 17, 1957, 729.)

Arne Kåss: **Two cases of rare malformations.**

Case 1. Bilateral anophthalmia with changes in the EEG.—The case of a 6-week-old female infant with bilateral anophthalmia is reported. She was the only child of healthy, unrelated parents. Normal pregnancy; no febrile illness or X-ray examination of the mother during gestation. In addition the child had a unilateral choanal atresia and bilateral dysplasia of the hip-joint. She was lively, did well and had no other signs of clinical cerebral palsy. An EEG taken at the age of 2 weeks showed a striking reduction, almost absence, of activity over the temporo-occipital and parieto-occipital regions. These findings are taken as evidence in support of the conjecture that, in addition to the anophthalmia, there is a deficient development of the optic areas of

the brain. The marked and relatively extensive findings resulting from the registration of activity over this part of the brain can possibly permit one to suppose that not only the purely visual areas of the cortex are affected, but also adjacent areas with other optic functions.

Case 2. Duplication of the stomach.—Duplications can occur anywhere in the gastrointestinal tract, from the base of the tongue to the anus, the most frequent location being the small intestine. Duplication of the stomach is a rarity. In this patient a large tumour occupying most of the left side of the abdomen was discovered by accident a few days after birth. Urography showed a displaced and deformed renal pelvis, and the findings were at first interpreted as being indicative of a renal tumour, probably malignant. Preoperative radiotherapy was administered without effect. The patient was operated on at the age of three weeks and a duplication of the stomach was found in the form of a cystic tumour. The tumour contained an opaque liquid, which gave a negative Kongo reaction, HCl/T.A. = 0/16. The duplication had no communication with the lumen of the stomach, but the musculature was common to both. Histological examination of the removed specimen showed a normal stomach wall with differentiated fundus and pylorus mucosa. There were no postoperative complications, and an X-ray examination made a few days after the operation showed normal emptying of the stomach.

Johan Olsen: **The initial temperature drop in the newborn.**

The purpose of this study has been to obtain a better knowledge of the initial temperature drop in the newborn. For the study a Microvolt clinical thermometer, for which is claimed an accuracy better than ± 0.2°C, was used. The measurements were carried out at the Maternity Hospital, University of Bergen. The average temperature in the delivery rooms was 23.8°C. The humidity of the air was not measured, but it is presumed to be fairly constant. The mothers were healthy primiparae or multiparae with no fever and an average rectal temperature of 37°C. All the deliveries were spontaneous and without anaesthesia. The study matter consists of 10 full-term healthy infants. Immediately after delivery the thermometer was placed in the rectum and fixed so as to remain in the same place during the course of the observation. The temperature was read every minute during 60 minutes. Immediately after the umbilical cord was cut, the infants were placed in a crib in the delivery room, without being washed, and covered with a diaper. Immediately after delivery the infants' average rectal temperature was 36.8°C. During the first 5 minutes the temperature drop was negligible, but from then on the temperature fell relatively quickly, dropping to an average of 34.5°C in the course of 35 minutes, that is to say, an average drop of 2.3°C in half an hour. In the remaining 25 minutes of the observation the temperature did not drop further, or the drop was merely negligible. To study the influence of a higher room temperature on the initial temperature of the newborn, a similar study was carried out on 10 full-term, spontaneously delivered infants, who were placed in an Armstrong incubator at 32–34°C with more than 80% humidity, immediately after birth. The average drop in this group was 1°C. As in the first group, the temperature drop occurred in the first 30 or 40 minutes and remained unchanged during the latter part of the observation. The initial temperature drop in the newborn commences in the course of the first minutes after birth, and can be presumed to be near its maximum at the end of the first half hour. This drop can be influenced by a higher external

temperature and must be considered as an expression of a transitory failure of thermoregulation in the newborn, since in all the cases observed the temperature had risen to 36.7°C within 6–12 hours following the end of the observation.

Aase Skogrand and Kristian Harnæs: **Cause of death in prematures.**

In the years 1954, 1955 and 1956, a total of 262 prematures were admitted to the Paediatric Department, University of Oslo. The overall mortality was 29% with the following distribution according to weight: less than 1000 g, 71%; 1001–1500 g, 46%; 1501–2000 g, 14%; 2001–2500 g, 23%. These figures should not be directly compared to those reported by other clinics. Most of the infants in our series were born in the Maternity Department, Rikshospitalet. The procedure employed there is that only those infants with a birth weight of 1500 g or less are systematically transferred to the Paediatric Department. Of the larger prematures, only those who are not doing well are transferred, that is to say, 60% of those with a weight of 1501 to 2000 g, and 30% of those with a weight of 2001 to 2500 g. The lesions found at autopsy were the following: intracranial haemorrhages 11 cases; atelectasis 12 cases; atelectasis with hyaline membranes 26 cases; pneumonia 11 cases; lung haemorrhages 12 cases; malformations 1 case; volvulus of the small intestine 1 case; intestinal perforation with peritonitis 1 case; hydrops foetalis 1 case. The different pathological findings were commented on, and it was pointed out amongst other things that atelectasis is a purely descriptive term which must not be interpreted as a cause of death. It was concluded that a significant decrease in mortality among prematures cannot be expected until a better knowledge is obtained of the factors which, apart from immaturity, lead to the production of hyaline membranes in the lungs, intracranial bleeding and lung haemorrhages.

O. K. Harlem: **Abdominal skin reflexes in newborn infants.**

According to well-known textbooks on neurology and paediatrics, the abdominal skin reflexes in newborn infants are present only in a relatively small number of cases and are of an irregular pattern. Two hundred full-term infants in the first week of life were examined and all of them were found to have abdominal skin reflexes of a definite pattern. A film illustrating the typical abdominal reflexes was shown. (Published in *Arch. Dis. Childh., 32*, 1957.)

G. Flottorp, D. E. Morley and M. Skatvedt: **The localization of hearing impairment in athethoids.**

Ten patients with the athethoid type of cerebral palsy and hearing impairment, aged from 11 to 28 years, were examined. Their physical involvement ranged from slight to severe. Pure tone audiometric examinations, air and bone conduction, were made. Tests of monaural and binaural recruitment, aural harmonic threshold tolerance range and speech reception tests using phonetically balanced material were given to each subject. In addition, signs of diplacusis and an idiophonic effect were noted. Each of the patients showed perceptive type hearing loss, more noticeable in the high frequencies. Every case showed signs of cochlear involvement. All were found to have loudness recruitment. All reported hearing the beats in the test of aural harmonics at a point which was lower than that found in unimpaired ears. Responses

to the phonetically balanced material of the speech reception testing were varied, but as a whole, correlation between the extent of hearing loss for high frequencies and speech discrimination was fairly close. The majority of patients showed intolerance for sounds at high intensity. In some cases diplacusis was reported and in others an idiophonic effect was noted in connection with the testing of aural harmonics. On the basis of the outcome of the testing, it was concluded that their hearing loss is of cochlear origin. This is contrary to the majority of opinions expressed by others, but previous studies have not included as extensive a battery of audiologic tests. (To be published in *Acta oto-laryng.*)

Jens Steen: **Acute glomerulonephritis in children.**

Cases of acute glomerulonephritis treated in the Paediatric Department of Ullevål Hospital during the period from 1950 to 1956 inclusive have been followed up. The relation of the disease to infections is shown, and symptoms and treatment are discussed. The clinical course of the disease is characterized by disappearance of proteinuria first (usually early) with subsequent normalization of the sedimentation rate, and finally (often late) disappearance of haematuria. Death during the acute phase of illness was never observed, and after two years of observation there were only 2 per cent that were not considered completely cured. (Published in *Tidskr. for den Norske Lægeforening*, 77, 894, 1957.)

M. Skatvedt: **Seizure patterns in children with cortical epileptogenic lesions in EEG.**

Of 360 epileptic children, 52.2% had cortical epileptogenic lesions as evidenced by the EEG (spikes, spike waves, sharp waves or a combination of these). Another 24.4% had bilateral synchronous typical or atypical spike waves, while 16% had normal EEG's and the remainder focal dysrhythmias (theta delta) or generalized dysrhythmias. In this study the cortical epileptogenic foci are correlated with the children's seizure pattern. The widespread localization of the foci often found is striking. In 52.6% of the cases the foci were circumscribed to limited areas, but in the remainder the foci were spread over large areas. Only 10.1% had foci in the anterior temporal region, against 50% in adults. The posterior temporal region was the localization in 11% of the cases, the frontal lobes in 6.4%, central areas in 16.5%, parietal in 5.3%, occipital in 3.2%. The remainder were more widespread, the largest group, 14.9%, having a temporo-parietal localization. Grand mal constituted the largest group, with foci spread over the whole cortex. Focal motor seizures show foci all over the cortex, but more frequently in the central regions. Focal autonomic seizures are quite frequent in childhood and are also represented by foci which can be found anywhere over the cortex. Only 4 of 188 patients showed automatism; 2 of these patients had foci in the anterior temporal region, 1 in the central region, and 1 had multiple foci. Akinetic seizures as represented by salaam seizures were found in 6 patients. The conclusion is that epilepsy and the localization of the epileptogenic foci are more varied in childhood than in adult life. It is difficult to predict the localization of the epileptogenic lesion from clinical findings.

Roald Rinvik: **Idiopatic hypercalcemia in infancy.**

A case of idiopatic hypercalcemia is reported. Although considerable retardation of both physical and mental development persisted, a certain tendency to improvement

was noted during one year of observation. This result suggests that treatment even in severe cases may result in reversal of some signs. Leukocytosis and splenic enlargement were observed during the first months of illness. This might suggest an infective origin of the illness, perhaps related to the cholesterol metabolism. (Published in *Ann. Paediat. Fenn., 3*, 3, 464, 1957.)

E. Esp: **Hypogammaglobulinaemia.**

The author reports a case of this disorder. As an infant the patient suffered from recurring infections. At the age of 8 months the blood gammaglobulin was determined, showing a level of 3% of total protein, instead of the normal 10 to 13%. The patient's parents and brothers had normal values. The patient received continuous prophylactic penicillin therapy and his condition was satisfactory. The gammaglobulin values were somewhat variable at first, but reached normal levels at the age of 1½ years.

Arne Kåss: **Reticuloendotheliosis—Cortisone treatment**

A 12-month-old female infant had a tumour over the outer part of the left upper orbital margin. Radiologically there was a polycyclical defect in the cranium. The histological findings were compatible with the clinical diagnosis of eosinophilic granuloma. The tumor decreased in size under X-ray therapy. Apart from a scanty papulose exanthema which the patient had had since the age of 8 months, her general condition was excellent. At the age of 17–18 months the clinical picture changed radically. The patient developed an oscillating fever, her general condition deteriorated, and there appeared over the trunk a granulomatous exanthema with prominent lesions; simultaneously the scalp became covered with greasy seborrhea-like crusts. She developed a stomato-gingivitis with loosening of the teeth. There was no hepatosplenomegaly but there was a moderate generalized lymph-node enlargement. Her serum cholesterol value was normal. Under cortisone treatment there was a marked remission of all her symptoms and a rapid improvement of her general condition. The patient was put on a low maintenance dosis, 18.75 mg daily; there was a reappearance of the tumour over the left eye, as well as of her seborrheic scalp lesions. The dosage was increaed and there was a new remission of her seborrheic exanthema. The tumour was also clearly decreasing in size after a few weeks. Nevertheless local radiotherapy was instituted, with good results. Her other symptoms are now completely quiescent and her general condition is excellent, approximately 3 months after the initiation of treatment with cortisone. The results of the skin and lymph-node biopsies agreed with the clinical diagnosis of reticuloendotheliosis. While the condition was first interpreted as an eosinophilic granuloma, it now seems logical to consider it a case of Hand–Schüller–Christian's disease, if one still wishes to group the clinical pictures of the reticuloendotheliosis in different syndromes.

J[illegible]geir Hvidsten: **A case of eosinophilic granuloma of bone.**

The evidence in favour of the essential unity of Letterer–Siwe disease, Hand–Schüller–Christian disease and eosinophilic granuloma of bone has been steadily accumulating. The similarity of the basic pathology has been reviewed by Wallgren in 1940 and by Jaffé and Lichtenstein in 1944. Attention has also been drawn to

cases with transitional features. The term eosinophilic granuloma of bone has been applied to destructive bone lesions, occurring chiefly in children and young adults.

Case report: A girl was admitted to the Children's Hospital in Bergen at the age of two years (17.12.1956). Her general health and development had been normal until 3 weeks before admission, when she got a head injury resulting from a fall on the floor. The physician some days later observed a soft swelling in the right occipital region. Some days before admission the face was asymmetrical, and palpation revealed a swelling of the left lower jaw bone. On admission the child appeared ill, and seemed very fretful. The temperature was normal. A moderate degree of nuchal rigidity was found. In the right occipital region there was a soft, smooth, fluctuant swelling, and in the left lower jaw bone, a tumourlike swelling. There was no enlargement of lymph nodes and no enlargement of the liver or spleen. The respiratory, central nervous and cardiovascular systems appeared normal. The laboratory findings revealed nothing but a slight hypochromic anaemia, and especially no eosinophilia. Radiographs of the skeleton showed numerous defects in the frontal and occipital bones, the jaw bones, in the pelvis as well as in the ribs and the bodies of the cervical and dorsal vertebrae. A biopsy specimen from the soft fluctuant swelling in the occipital bone consisted of soft yellow-red granulomatous masses. The microscopical picture revealed macrophages, numerous eosinophilic polymorphnuclears and giant cells. Diagnosis: Eosinophilic granuloma. Roentgen therapy was then administered against the different bone lesions. Later roentgen examinations, however, showed many new osseous lesions in the previously affected bones. Cortisone therapy was also administered without any effect. Five months after admission, new radiographs disclosed complete destruction of sella turcica and severe osseous lesion of the sphenoid bone as well as complete collapse of the body of the twelvth dorsal vertebra. The severe lesions of the vertebral bodies in this case will probably lead to compression of the spinal cord. Finally further progression of the disease in the pituitary region later on may be responsible for a Hand–Schüller–Christian syndrome.

Valborg Torp: **Children with handicaps.**

The amount of children with handicaps is certainly larger than our statistics show. The author points out that children with handicaps must be brought out of their isolation and given efficient treatment, as well as facilities for learning and employment. For this work, specially trained personnel is required. There is a shortage of such personnel in this country.

J. Luhr and K. H. Torp: **The value of placental examination in the control of status of the newborn.**

Among 407 births in a period of two months 123 placentas were submitted to special examination. The significance of such study in the control of status of newborn infants was stressed. Brief descriptions were given by way of illustration of two cases of serious haemorrhage from the foetal part of the placenta, blood transfusion being necessary, and two cases of intra-uterine underdevelopment, considerable changes in the placenta being simultaneously demonstrated. (Published in *Nordisk Medicin*, 57, 923, 1957.)

Kr. Harnæs: **Haematuria—a follow-up.**

Even in a well-equipped hospital where one can carry out all the necessary examinations of children with haematuria (urography, retrograde pyelography, cystography, urethrography, cystoscopy, urethroscopi plus blood and urine analysis), one will still find a certain number of cases where one fails to arrive at a topographical diagnosis, and where one must be content with the purely symptomatic diagnosis of haematuria. In the period from and including 1947, up to and including 1956, 34 patients at the Paediatric Department, University of Oslo, received this diagnosis. It was inquired by letter whether the haematuria had persisted after their stay in hospital. The age distribution was from 1 to 12 years and there were 23 boys and 11 girls. The time elapsed since they were seen in hospital varied between ½ and 10 years. In 22 of the patients there has been no recurrence of the haematuria and they have been in good health. The haematuria has recurred in 7 of the patients. No answers were received in 5 cases. The 7 cases with persistent haematuria were examined anew. In one case a ureteral calculus was discovered, another was found to have a hypertrophic and vascularized colliculus in the bladder as a probable explanation for the haematuria, a third patient had an ulceration of the urethra and in a fourth the condition was interpreted as being a chronic nephritis. In three cases the second study failed to reveal a cause for the haematuria.

KR. HARNÆS, Oslo, Norway.

Section of Pediatrics and School Hygiene of the Swedish Medical Society

Meeting October 11, 1957

P. Karlberg: **Lung functions during the neonatal period—a comparison with those of adults.**

(Published in *Acta pædiatrica.*)

G. Berglund: **Fibrinolytic activity during the neonatal period.**

The fibrinolytic activity has been investigated by means of the fibrin plates of Astrup & Müllertz. The investigation was made on umbilical artery blood in 48 normal cases. In almost half of these no fibrinolytic activity could be demonstrated, in the remaining cases there was found a slight and in some cases a moderate activity. The fibrinolytic activity was examined in children during the first week of life, decreasing sharply during the first three days and later becoming undetectable. A number of children with asphyxia and neonatal erythroblastosis were examined. In these cases the fibrinolytic activity was noticeably higher than in the normal material, in certain cases even increasing during the first days of life, only to decrease later. Whether the fibrinolytic activity, which can be shown in the umbilical cord blood in healthy children is formed by the fetus or whether it is passively transferred from the mother is not clear. The examinations of the asphyctic children and children with erythroblastosis show, however, that the child can develop a fibrinolytic activity itself.

G. Bloom, H. Dunér, B. Pernow, J. Winberg and R. Zetterström: **Spontaneous histamine shock in urticaria pigmentosa.**

(Published in *Acta pædiatrica.*)

M. Barr, S. Kraepelin and R. Zetterström: **Acute hemolytic episodes in children with allergic diseases.**

Account of the clinical picture in two allergic children with acute hemolytic attacks in connection with asthma, allergic rhinitis or eczema. The hemolytic reaction was found to be caused by eating of minimal amounts of food or the inhalation of substances which are known to give antigenic reactions in sensitized individuals. The hematological findings in one of the children were compatible with the diagnosis of chronic acquired hemolytic anemia which is exacerbated when the patient is exposed to the material which gives an increased hemolysis. Some sort of allergic reaction is suggested as cause of the abnormal hemolysis after exposure. The similarity with favism is discussed.

Discussion.—*R. Lagercrantz:* It was interesting to hear that Sjöstrand's carbon monoxide method for the determination of intravascular hemolysis was tried in Case 2. This is thought to be more sensitive than the other methods which are used. Was it tried in the first case and has it been tried in other cases where intravascular hemolysis after exposure to allergens was suspected? It is possible that hemolysis depends on an antigen-antibody response on the blood cell's surface. There are methods to study such mechanisms. One sensitizes the blood cells either with an antigen or with a deficit of antibody. It would be interesting to try such a so-called conditioned hemagglutination or hemolysis reaction in these cases.

Ove Broberger: **Exanthema subitum and febrile convulsions.**

Thirty cases of exanthema subitum were recorded among 153 cases of febrile convulsions treated in the children's clinic, Karolinska Sjukhuset, Stockholm, during the years 1952–1957. A higher incidence, 21.2–39.1%, was recorded during the last two years, when the cases with febrile convulsions were thoroughly investigated with respect to blood picture and exanthema of short duration. The material was analysed mainly with regard to temperature conditions, age incidence and heredity. The temperature conditions, with a rapidly rising, very high temperature, seem to favour the generation of convulsions. The 30 cases of E.S. differ from febrile convulsions in general in two respects. They occur at younger ages and they lack heredity for febrile convulsions. The high incidence of E.S. in the material, the lack of heredity and the age distribution indicate that E.S. exhibits a more specific cerebral influence than could be explained solely on the basis of fever. The investigation of the spinal fluid revealed no signs of true infectious encephalitis or meningoencephalitis, but could agree with a paraencephalitic (toxic allergic) process.

Meeting December 7, 1957

L. Hamberg: **The caries problem—an information and an appeal.**

Dental caries has an almost 100% prevalence in our country. Even our 2-year-olds are affected up to 20%. When the children start school, one can find only 2 or 3

children per 1000 who are caries-free. Even earlier it was suspected that a relation must exist between our consumption of highly-refined carbohydrates and the increasing incidence of caries. No dependable figures were available, however, until the results of the Vipeholm studies were finished in 1953. These showed a clear relation between oft-repeated carbohydrate consumption and dental caries. And the degree of that consumption is frightening! We consume bon-bons, caramels, chocolates, etc. in the amount of 550 million kronor per year, pastry for about 220 million kronor per year, and there are 4000 tons of sugar used each year for tablets and pastilles! The Swedish people's cost of dental care has been estimated at 250 million kronor per year. This disease has become a medico-social and economical problem of enormous dimensions. Of the caries-producing factors the exogenous ones have claimed the greatest interest and it is especially the deposits, so-called dental plaques, on the teeth which have become the subject of more detailed examinations: where these deposits are found, the caries first appear. These pasty, often carbohydrate-rich deposits provide an excellent substrate for bacteria where streptococci and diplococci are predominant in number, but where also many other types such as lactobacilli are found, especially if carbohydrates are added in great quantity. These carbohydrates are broken down by the bacteria through enzymatic activity, as a result of which the fatal acid for decalcification is liberated. The fight against the increasing frequency of caries must be intensified. The general public must be informed concerning the significance of food, and the necessity of good oral hygiene. The Dental Prophylaxis Group and the Royal Board of Health have engaged themselves in this information program. The necessity of better teamwork between the doctors and dentists in preventive childrens' health care is emphasized. To add the diagnosis of dental caries to the main illness on the charts in the children's hospital should certainly be a worthwhile and thought-provoking enlightenment for the parents. From the research viewpoint it is important to be able to care for children with a high caries activity in the hospital. The addition of fluorides to suitable vehicles is viewed as significant in relation to reducing the incidence of caries.

Discussion.—*G. Herlitz:* If I understood Dr. Hamberg correctly he said that diabetics have an impressive susceptibility to caries during their entire life span. At least in the case of children I wonder if that is correct. I have earlier had occasion to be occupied with that question, and found in some 40 children with diabetes of different ages who were examined that their incidence of caries was not greater than in healthy children; on the contrary, the opposite was true. It was also shown that the amount of reducing substance in the saliva of diabetic children did not vary with the blood sugar level, but held itself constant at the same value as in healthy children, independent of the blood sugar level. The observation was shown to have been made earlier by Babkin, who worked with adults. The salivary glands are thus seen to withhold sugar selectively in diabetic children, even with very high blood sugar levels. The lactic acid content of the saliva increases quite rapidly after a meal, but if the children rinse the mouth carefully after eating, this increase is absent. I also found that a noteworthy increase of the lactic acid content in saliva was absent if the children completely emptied their mouths of saliva without rinsing following a meal, namely by spitting twice effectively. — *O. Naglo:* The propaganda against the eating of sweets certainly has great significance. In one child welfare center where such propaganda has been carried on, the incidence of caries has decreased significantly. There one often finds caries-free milk teeth in 4–5-year-olds. No other prophylactic precautions

against caries have been used other than propaganda against candy-eating. — *A. Johansen:* Observations over many years in two child welfare centers in Götebo g with a clientele of varying social status, have shown that the incidence of dent al caries was noticeably less in the center with mothers in a better social position wi h more time and interest for caries prophylaxis and better desire for cooperation. In those cases where caries was found, the mothers receive a written recipe for "dent al diet" with a predominance of vegetables, fat, protein and mineral-rich foods, and wi h forbiddance of all sweet breads and candies. In addition rules for daily dental care, mainly according to the Dental Prophylaxis Group's "reminder list". The same regime is applied to the clientele in Vidkärr's children's home, which is recruited mainly from poorly situated social groups. At the time of the child's discharge, the person responsible for his care receives the same sort of recipe and reminder list which he (she) often may write out himself. — *H. Jelke:* During the period of one year I noted all patients in consultation with completely healthy teeth, a total of 24. None of the patients had attempted an especially rigorous regime with regards to caries prophylaxis. It was shown that 14 of the cases were diabetics. Despite the fact that the diabetic clientele did not comprise more than ca. 1% of the total of those seeking care during the period under question, they corresponded to 60% of the number with totally healthy teeth. All these diabetic patients carry out their programs to the letter, and because of this one has reason to be concerned with a minimum of extra carbohydrate consumption between meals. — *K. Kaijser:* A propaganda against the eating of sweets can certainly be more effective if it makes a differentiation between an occasional intake of sweets once a week and a constant intake. I believe that the danger in moderate eating of sweets does not primarily exist in that it eventually damages the teeth, but rather that it can drive the individual toward a "narcomania"—a constant eating of sweet things. The injurious effect of this on the teeth can be regarded as indisputable. But I believe that the propaganda would gain through not demanding total abstinence from sweets and the like.

***B. Karlsson:* Paroxysmal headache in children.**

One designates as paroxysmal headache the trouble in 23 patients, 12 boys, 11 girls, all of whom have not only attacks of headache but also EEG changes with so-called epileptogenic attack activity. Thirteen patients show focal cortical attack activity with spikes or sharp waves with one exception localized temporally. Generalized breaking-through attack activity of the character of irregular spike-and-wave or sharp-and-slow-wave activity was seen in 20 patients. Photo-stimulation was essential for the appearance of the latter type of attack activity. Further noteworthy examination results are the appearance of obvious psychic symptoms in more than half the cases as well as reading disturbances in 7 patients. There is a positive family history for headache in 13 cases, pronounced dizziness in 3 cases, epilepsy in 4 cases and psychic disturbances in 3 cases. Birth history was noteworthy in 6 patients. A summary of the symptomatology shows that headache as a rule is combined with one or more of the symptoms of nausea, vomiting, abdominal pain or sleepiness. Treatment with difhydan was used in 13 patients, and the result can be regarded as good in 11 cases.

Discussion.—*B. Bille:* In an investigation of the incidence of migraine among all school children, that is about 9000 children, in Uppsala between the ages of 7 and 15 years, it was shown that about 3.5% had migraine. As criteria for the diagnosis of

migraine, paroxysmal headache was used along with at least two of these four symptoms: one-sided headache, nausea or vomiting, visual disturbances, and positive heredity (parents or siblings).

B. Hellström: **Is it possible to eliminate retrolental fibroplasia?**

All cases of retrolental fibroplasia in Sweden have to be reported to the Royal Board of Health. The incidence of the disease in this country is diminishing, but as this decline did not seem as dramatic as could be expected, this study was initiated. The charts of all children born 1954, 1955 or 1956 in whom the disease had been reported were studied. Forty-two cases had occurred; 38 of these had received extra oxygen, some of them on doubtful indications and, as it seemed, for an unnecessary length of time. Three cases had not been treated with extra oxygen; two of these were entirely reversible, the third was almost blind. In one case no reliable information as to incubator treatment could be obtained. It was pointed out that there may be diagnostic difficulties in cases observed only in the cicatricial phase; congenital toxoplasmosis and encephalo-ophthalmic dysplasia had presented a similar picture in two cases. If a more rigorous restriction in the use of oxygen is adopted it seems as if the disease can be reduced to a few per cent of its former incidence. Sporadic cases may continue to occur. Those found in prematures who have not received extra oxygen deserve especially thorough study.

Discussion.—*B. Hamne:* Don't risks also exist in refraining from giving oxygen? Even if the attack of cyanosis ends spontaneously, one may ask with dread how long the immature cell in the central nervous system can stand to be exposed to inadequate oxygen. Perhaps the cerebral damages will increase if we become too scared of using oxygen therapy. — *B. Hellström:* A premature showing definite signs of hypoxia, such as general cyanosis should of course be treated with oxygen. In larger groups of prematures, where restrictive principles in the use of oxygen have been adopted, the mortality has not increased.

P. Karlberg, E. Adams, G. Kock and J. Lind: **Pulmonary function during the newborn period.**

(To be published in *Acta pædiatrica.*)

Discussion.—*K. Kaijser:* One gets the impression occasionally that respiration in the newly-born child is initiated with more difficulty in Caesarian section than after normal delivery. I have conceived this to be on the basis of a normal delivery, through its mechanical effect on the child, representing a better prerequisite for the lungs in that in a quick and correct manner they are filled with air after the child's delivery. Can that viewpoint receive support through the examinations carried out by Dr. Karlberg?

Engström, P. Karlberg, G. Koch and S. Kraepelin: **A sensitive method for determination of provocation test in bronchial asthma.**

Account of the preliminary results in measurement of the air resistance in the respiratory passages before and after attempt at provocation is reported. The attempt at provocation is carried out in an allergic examination of bronchial asthma to

test whether a manifest allergy is present. These are usually carried out as an inhalation test. The result is determined through usual clinical examination. Since it is probable that the slightest reactions can be overlooked in that procedure, the authors have measured the air resistance in the respiratory passages before and after provocation. Respiratory volume, air flow and intra-esophageal pressure have thereby been registered simultaneously. It has been shown that the more pronounced the clinical symptoms are, the greater is the increase of the airway resistance. Also, with mild symptoms one finds a definite increase of the airway resistance without simultaneous clinical symptoms. The described method gives increased possibilities of determining manifest allergies.

H. O. Ahnlund, H. Ekelund and P. Rudström: **Local pulmonary emphysema in small children. Four operated cases.**

Account of a typical symptom complex with respiratory difficulties caused by local emphysema within a lung lobe, usually an upper and most often the left, with simultaneous collapse of the inferior lobe on the same side. Genesis is discussed. The change is congenital and depends on the malformation of some part of the bronchial tree. The role of infection as a complicating factor is pointed out. Four operated cases are described. In three cases lobectomy in somewhat older children gave good results. In one case pneumonectomy in an infant who postoperatively developed retention of secretions and died with acute lung atelectasis. In conclusion the risk of positive pressure breathing in children with this type of respiratory difficulty is pointed out.

O. Celander and G. Haglund: **Salicylate poisoning in infants.**

Short exposé of the incidence of cases of poisoning with salicylic acid and its pharmacodynamics. The pathophysiological process in poisoning, clinical picture of poisoning, diagnosis and differential diagnosis and course are discussed. Alternative methods of treatment, with a special account of what is to our knowledge a hitherto unproven type which we have practised with relatively satisfactory results. In conclusion several comments on the possibilities of decreasing the frequency of poisoning cases with salicylate preparations.

G. Sterner: **Adenovirus infection. (Views on acute upper respiratory tract infections in children.)**

Somewhat over 200 children with acute respiratory infections have been examined since October 1954 for the appearance of virus in the feces. Cytopathogenic agents belonging mainly to the group adenovirus (types 1, 2, 3, 5 and 7) have been isolated from one-third of the cases. Serological tests showed that in many children the adenovirus infection proceeded simultaneously in that clinical symptoms of a respiratory infection were present. The examination gives rise to a discussion of the problems which are met in the attempt to discover the etiology in isolated cases of respiratory infections in children.

V. Oldfelt: **Incontinentia pigmenti. (Bloch–Sulzberger's syndrome.)**

Account of three cases of this probably hereditary and sex-linked disease, or really polydysplasia, which predominantly affects girls and evidences itself: (1) In the ne-

natal period with bullous eruptions which later progress to hypertrophic, wart-like skin changes and finally to characteristic, longish, hyperpigmented small spots on the body, mostly on the flexor surfaces of the arms and legs. The prognosis regarding the pigmentation is good since it blanches over the years. (2) It is often combined with delayed and deficient dentition, in one of the actual cases almost an adontia, i.e. the boy (unusual: only 4 of 80 published cases are boys) has most sparse permanent tooth rudiments according to X-ray and only 10 decidual teeth at 4 years of age. (3) There often appears an *alopecia* areata. (4) Often spasticity and oligophrenia and other diverse neurological manifestations. (5) Often among them eye anomalies. Occasionally an eye has been enucleated on the basis of suspected glioma. Often strabismus and decreased vision, anisometropy and others. — The important thing is that one *recognizes* the syndrome. It can be confused with dermatitis herpetiformis (which should be treated with sulfa) and hereditary epidermolysis which has a worse prognosis. Furthermore the eyes, teeth, and psyche should be observed in these cases. No case in the Swedish literature until the present, but 3 Danish reports. In the acute phase there is a marked eosinophilia in the blood and skin changes. PAD shows typical pigmentation position changes—incontinence—from the epidermis down to the corium.

G. Hedenström, G. Huldt and R. Lagercrantz: **Toxoplasmosis studies.**

Report of 52 cases of congenital toxoplasmosis and 32 cases of acquired toxoplasmosis. In all cases high specific antibody titers have been demonstrated. In 4 cases of congenital and 1 case of acquired toxoplasmosis the parasite has been isolated. In this series appears the classical triad of chorioretinitis, hydrocephalus, intracerebral calcifications in 12 cases, 7 dead within the first half-year of life, of those living 3 have convulsions and all are psychically underdeveloped. The combination of chorioretinitis and intracerebral calcification appeared in 11 cases, none dead, 6 have convulsions and 5 are psychically underdeveloped. Chorioretinitis and hydrocephalus: 4 cases, 2 dead, of the living 1 psychically debilitated. Hydrocephalus with or without cerebral calcification: 3 cases of which 2 are dead. Among the remaining 22 patients, all now living, 15 had only chorioretinitis, one microcephalus and 6 lacked the "classic" symptoms but had convulsions and/or psychic underdevelopment. The children with chorioretinitis were bothered but not invalidized by their eye damage. It is especially interesting that at least 9 children were psychically normal and only had minor residual symptoms after their illness (chorioretinitis in 9 cases, petit mal in 1 case).

Acquired toxoplasmosis shows three separate stages in animal experiments: (1) local inflammation and regional lymph gland enlargement, (2) parasitemia and deposition in different organs, (3) so-called terminal colonies which only in the exceptional case cause tissue damage. In this series 7 children had the disease picture which is known from toxoplasmosis in adults: lymph gland enlargement with signs of irritation of the reticulo-endothelial system and a blood picture simulating that in infectious mononucleosis. Signs of a slight meningoencephalitis occurred in 1 of these patients and chorioretinitis in one. Of the remaining cases 22 had a disease picture which now cannot be interpreted as toxoplasmosis, and 3 have been completely symptom-free (contacts of known cases).

The preliminary results of the investigation indicate that congenital toxoplasmosis, although often serious, can progress undiscovered and give relatively unimportant residual symptoms, and that acquired toxoplasmosis in children appears to have a

similar course to that in adults. On the basis of the disease's endemic character with numerous cases progressing sub-clinically, great caution must be observed before one places the finding of high titers in relation to a clinical disease condition.

R. Lagercrantz: **Serious infections in the antibiotic era.**

In the antibiotic era, during the years 1951 to 1957, 67 patients died with infectious diseases in the Pediatric Clinic, Karolinska Sjukhuset. These comprised 19% of the deaths. Cases with serious malformations, malignant tumors and pancreatic fibrosis have been excluded. There remained 24 patients who died with primary infectious diseases. Twelve of these, including 5 new-borns and 6 infants, had infection of the lungs and air passages. During the period there were altogether 6 cases of sepsis registered, of which 2 resulted in death. The number of registered cases of purulent meningitis was 66 of which 5 resulted in death. One child died from tetanus and 4 with congenital toxoplasmosis. Ten of the 24 patients were new-borns. In these the classical symptoms of infection such as fever and increased sedimentation rate were often absent, especially at the beginning of the illness. In a total of 17 cases the diagnosis of a lethal infectious disease was made too late. The mortality in infectious diseases among the prematures was surprisingly low. Prophylactic antibiotic treatment is considered to be contra-indicated also in the neonatal period. With examples it is shown that hospital infections are often antibiotic-resistant. In 11 of the 24 cases the infection was believed to have been hospital-caused. In altogether 14 cases Staphylococus aureus was demonstrated. Early diagnosis, taking of bacteriologic samples (repeated in complications), control of the antibiotic concentration in the body fluids (with the help of the simple "patch method") and good hospital hygiene are all requirements to make possible a further reduction in the mortality in infectious diseases. In those cases which run a fatal course, specimens for bacteriologic culture should be taken at post-mortem examination as soon as possible after death. One thereby obtains—as is shown with an example—the possibility of carrying out a complete epicritical reasoning. One should also carry out such examinations in uncertain cases of death, especially in the neonatal period, where infectious diseases can play a greater role than many now believe.

Discussion: *R. Lundström:* The cases of mortality in the speaker's infection material appear in no small part to have reference to patients with a condition of poor immunity. Work has recently appeared which shows that in experiments on mice no small synergistic effect can be won through combination of antibiotics and gammaglobulin in illnesses caused by, for example, Pseudomonas, Proteus and Staphylococcus. Such combination therapy has been put to practice among others at the Kronprinsessan Lovisa's Children's Hospital in cases of more severe infections with apparently favorable results. Newly-published reports from other places show cases where they have failed when using only antibiotics, but complimented with big doses of gammaglobulin a probably life-saving effect has been produced. These reports ought to encourage further attempts in such categories of cases of infection which were presented in the report.

T. Thysell: **Occult sinusitis in temporal relationship with grave mental disturbances in boys.**

We observed in 1957 three cases of occult sinusitis in boys. In time relation with sinusitis the boys presented quite alarming mental symptoms of such a type which

are usually described in adults who have infections. One of the circumstances responsible for the explanation of the etiological factors in these three cases is the fact that all three boys come from defective and unsatisfactory home environments. Two of them are in puberty and the third in pre-puberty. The latter has also, as does his mother, a disturbance of motility which, however, neither in mother or child is neurologically demarcated as any special neurological complaint. The purpose of the association is only to draw attention to the fact that occult sinusitis can be found in children who are admitted in abnormal mental states. In all three cases the children's behaviour became normalized at the same time that the sinusitis condition disappeared roentgenographically.

M. d'Avignon: **A medical and social analysis concerning cerebral palsy (Cp) in children and adolescents in the Stockholm region.**

A short review of Cp-care organization in the Stockholm region. An analysis has been made of the entire Cp-population in the age group 1–20 years which one could find in the area. In a population of 328,300 in this age span 366 (402) cases have been found and worked up, which should speak for an incidence of Cp-children of 1.2 per 1000 children. It is, however, only in the age group 7–13 years that most Cp-cases have been found, and if one reckons the frequency according to the incidence of Cp-children of that age, there would be 1.6 Cp-children per 1000 children of the same age. Distribution of the type of injury shows 80% pyramidal tract injury (so-called spasties). The remainder are divided among other types of Cp. Conceivable etiology of the patients' injuries are discussed thoroughly. Barely 55% of the children have an intelligence quotient of 75 or over. The distribution of the intelligence among the different types is discussed. The incidence of epilepsy in the various types is also discussed. One attempts through correlation between the degree of injury and intelligence to determine the prognosis with thought to future possibilities for care and finds that one third of the patients have a medium prognosis, while among these only 17% have very good chances to be able to compete in the labor market in the future. Treatment and the effectiveness of the social worker is discussed. The demand for good working power here is believed to have further increased. Questions of placement in school are touched upon and finally the difficult problem of training for a trade and placement in the labor market is considered. A large group have no employment at all. Many Cp-adolescents would need to be placed in protected workshops, but such suitable ones are not to be found. Large deficiencies also predominate with regard to trade guidance and training.

M. d'Avignon, Stockholm, Sweden.

Acta Pædiatrica **47**: 332—336. May 1958

BOOK REVIEWS

Sven Roland Kjellberg, Nils Olof Ericsson and Ulf Rudhe: **The Lower Urinary Tract in Childhood.**

Almqvist & Wiksell/Geber AB, Stockholm. 298 pages, 265 figures. Price Sw. Kr. 80.

This book is not intended to be a textbook or handbook with a complete account of all diseases and malformations which occur in the region. Its purpose is to stimulate interest for urological problems in children through presenting a detailed account of personal experience regarding certain of the most important problems and the methods of examination used. The material consists of 1461 children, of whom 1155 have disease conditions of the lower urinary tract, while the remaining 300-odd children represent control material with normal lower urinary tracts. The book attempts to correlate the clinical and roentgenological findings, but also gives a review of the results of treatment in certain conditions.

Micturition urethrocystography is considered to be an indispensable method of examination if one wants to study the physiological or pathological course of a micturition. This cannot be accomplished with only endoscopy or urography. The technique of micturition urethrocystography, as it has been devised by the authors, is described in detail. A barium suspension has been used as contrast material and is injected into the bladder via a urethral catheter. For retrograde urethrography a medium of the perabrodil type has been used instead. Pictures have been taken simultaneously in two planes, partially frontal and partially purely lateral projection. An automatic serial roll-film changer has been used with exposure of 3–5 seconds interval. Infants were examined while lying down, older children sitting in a specially-constructed swing. The technique of endoscopy is also touched upon.

Ectopic ureters and ureteroceles are discussed on the basis of 45 cases of which a few were of the unusual type with simple ectopic ureters bilaterally. Among other things the possibility is pointed out that with micturition urethrocystography an ectopic ureter opening in the urethra can be demonstrated on the basis of urethro-ureteral reflux. Principles of treatment and their results are discussed. With duplication of the ureters and kidneys pelvis, which is so common in ectopic ureters and ureteroceles in children, heminephrectomy is recommended with resection of the respective ureter and eventual ureterocele. Heminephrectomy has also been carried out bilaterally. Neurogenic bladders have been discussed also with regard to the upper urinary tract but the main interest has been directed to the sphincter's manner of reaction and to the reflux. The treatment has been markedly conservative surgically, with bladder neck resection in cases suitable for it, and with strict indications for definitive intervention in the form of implantation of the ureters in an isolated loop of ileum, so-called cutaneous uretero-ileostomy, or other larger procedures. The diagnosis of *congenital bladder neck obstruction* must be made by the process of exclusion and only after micturition urethrocystography. In many cases of suspected bladder neck obstruction other anomalies have thereby been met with which were the main causes for the symptoms while the bladder neck obstruction was of less importance. Cases of (mos

unusual) spontaneous bladder perforation are described. In *urinary tract infections without obstruction* certain typical changes or manners of reaction in the bladder and urethra have been met with. A complete review is given of the studies of the reflux phenomenon from the viewpoint of a possible sphincter function at the ureters' distal ends. Reflux occurs in 34% of infections without obstruction but in not one case of the control material. *Urethral valves* are discussed most thoroughly on the basis of 52 cases. The previously prevalent division into types is criticized. In all cases a pathological fold from the ventral urethral wall has been the principal cause of obstruction. Treatment should include resection of that fold and not merely the collicular folds which were previously viewed as forming the valves. The valve concept is expanded somewhat and the material includes valves of various degrees of obstruction. Principles of treatment and their results are discussed. The re-examinations comprise mainly the late result with regard to the lower urinary tract. Only 2 of 40 operated patients have died. The relationship between valves and enuresis is discussed briefly with preliminary reports of the results of surgical treatment. *Urethral strictures, polyps, diverticuli* and *colliculus hypertrophy* are touched upon in short chapters. Cases of *intersexuality* and *hypospadias* are treated primarily from the roentgenological-anatomical view-point. All cases of high-grade hypospadias have had a vagina emptying into the urethra. *Enuresis* has been investigated in 598 children with regard to the appearance of anomalies of the lower urinary tract which could conceivably represent an etiological basis. In purely nocturnal enuresis the findings in the lower urinary tract were normal in 50%, in combination with diurnal enuresis in only 34%. Urethral valves are seen in about 4%. Definite organic causes for enuresis are thought to be present relatively seldom in pure nocturnal enuresis, but still more often than was usually believed. In diurnal difficulty the frequency of suspected somatic causes is significantly higher.

This is an outstanding work which does honor to both the authors and the publisher. It should not be missing from any urological or pediatric library.

Physiology and Pathology of the Kidney.

British Medical Bulletin, Vol. 13, Jan. 1957. 74 pages. Price £1.

This volume, written by English clinicians, deals with recent progress in the concept of renal function. It is devoted mainly to the study of metabolic effects of renal disorders, a study, as Robert Platt states in his introduction, "starting from the concept of the kidney as a homeostatic rather than an excretory organ".

McCance & Widdowson stress the necessity of interpreting renal function at any age in relation to the demands imposed on the kidney. The current comparison of one age with another is often of but little interest. The subject is exemplified by studies on protein and NaCl metabolism in newborn infants. Black & Emery concisely summarize investigations made by themselves and others giving clear-cut evidence that renal excretion of potassium is mainly effected by tubular secretion. Finally, they notice that "an excretory mechanism based on secretion may be more adapted to the regulation of an intracellular cation than one based on filtration". Wrong gives an extensive review of the different possibilities for an efficient volume control of body fluids, and is personally inclined to postulate the existence of a special "volume receptor"—although he does not tell us where it is located. He stresses the necessity of differentiating between the syndrome of dehydration with inelasticity of the skin etc. which is due to shrinkage of extracellular space and hence loss of sodium, and

pure water deficit which does not result in this picture unless very severe. The problem of potassium deficiency, as complicated as clinically important, is unravelled by MILNE, MUEHRCKE, & HEARD. They state that changes of distal tubular function apparently due to intracellular acidosis are most characteristic of potassium deficiency. DARMADY & STRANACK illustrate their article on microdissection of the nephron with several plates demonstrating the site of the anatomical lesion in different conditions, especially those with damage of the tubules. HARRIS gives an account of the latest contributions to the problem of renal amino acid excretion in cystinuria, galactosemia, and Hartnup disease. The article on nephrosis by SQUIRE, BLAINEY & HARDWICKE mostly deals with the problem in adults, but also contains much of interest for the pediatrician. STANBURY successfully analyses the intricate problem of azotemic renal osteodystrophy and comments especially on rickets and osteomalacia, osteitis fibrosa and osteosclerosis, which all may be seen in the same patient at different times. Interesting, though of less importance to the pediatrician, are three papers on hypertension written by FLOYER & LEDINGHAM and WILSON & ABRAHAMS respectively. MACPHERSON & PEARSE describe the histochemical changes in the potassium depleted kidney, MCGEOWN & BULL write on the formation of urinary calculi, MURRAY & TRESIDDER on renal angiography and STEINER on venography in relation to the kidney. The volume is concluded by KENNEDY with a survey of the effects of old age and over-nutrition on the kidney.

This issue can be recommended as fascinating reading.

Jan Winberg

***Anaesthesia.* A Symposium.**

British Medical Bulletin, Vol. 14, pp. 1–68, 1958.

A number of articles in the present symposium reflect the collaboration between anaesthetists and workers in the basic medical sciences and in physics. The symposium includes sixteen papers, preceded by an introduction by the well-known JOHN GILLIES, which gives a good view of various important trends in anaesthesia today. Thus D. WHITTERIDGE gives a very comprehensive paper on "Effect of anaesthetics on mechanical receptors" in which many of the observations made clinically when volatile anaesthetics had been used get their proper physiological explanations. "Biochemical disturbances associated with anaesthesia" by J. D. ROBERTSON is a good paper which covers aspects of acid-base imbalance of respiratory and metabolic origin, changes in cell metabolism, renal and hepatic function, as well as changes in water and electrolyte balance. The author has succeeded in covering this subject in six pages without tiring repetitions. The list of references seems to comprise most of that which it is worth while to read on the subject. H. G. EPSTEIN of the Nuffield Department of Anaesthetics, Oxford, has written an interesting article on "Principles of inhalers for volatile anaesthetics". The author has a tremendous knowledge of the physical characteristics of anaesthesia apparatuses and bio-physics of anaesthetic agents, and his article contains much valuable information and should be read by every anaesthetist. A short, but very informative paper by CHURCHILL-DAVIDSON on recent developments in the muscle relaxants discusses the mode of action and abnormal response to non-depolarizing (D-Tubocuararine) and depolarizing (succinylcholine) agents. The author concludes that the commonest cause of prolonged action to a particular relaxant is an overdose of the drug.

Carbon-dioxide homeostasis in anaesthesia is always a big problem and has received

a lot of attention during recent years. E. A. PASK has covered this subject in many aspects and the article reflects the author's great experience. Of special interest is his review of CO_2 homeostasis in hypothermia. From theoretical and experimental evidence produced in the literature he cannot find any reason for monitoring a low pCO_2 during hypothermia. A somewhat different opinion is expressed by G. B. LUCAS in "Hypothermia in surgery: the present position", in which he states that the most important part of the technique "is to overventilate the patient deliberately".

Other subjects covered in the symposium are "Electrographic monitoring of Anesthesia" by B. D. WYKE and "Neonatal Anaesthesia" by JACKSON REES. Both articles show the authors' large experience in their respective fields and can be highly recommended for reading. That also applies to all other articles not mentioned in this review.

O. N–r.

H. Birkhäuser and H. Bloch: **Advances in Tuberculosis Research. BCG. A Discussion of Its Use and Application.**

S. Karger, Basel and New York, 1957. 316 pages, some figures and tables. Price Swiss fr. 42.

The 8th volume of the series "Advances in Tuberculosis Research" is devoted to a discussion on BCG vaccination, in which some twenty experienced and competent authors have contributed. An attempt has been made to emphasize the controversial questions concerning BCG, to present studies in progress and discuss crucial problems which are of theoretical and practical importance. Supporters of BCG vaccination as well as its opponents have been given a fair opportunity to stress their respective opposite opinions. Some of the chapters are especially informative and well-written, and among these the reviewer would mention in particular G. Dahlström's on "Clinical Considerations in Vaccination against Tuberculosis", K. Birkhaug's "Methods of Vaccination", de Assis' "Oral Application of BCG", and D'Arcy Hart and co-workers' report of the British Medical Research Council's trials. It is unfortunate that the Brazil method of repeated peroral administration of giant doses of BCG, irrespective of the status of tuberculin sensitivity before vaccination, has not been sufficiently tried outside Brazil to permit an adequate evaluation of its efficacy; this would be the method of choice for mass-vaccinations in countries with high tuberculosis morbidity. The notorious opponent of BCG, Dr. J. A. Myers of Minneapolis, has given an account of his objections and criticism of the use of BCG. He says: "A carefully controlled study has never been conducted in the slightest way comparable to what has always been demanded by way of control in other fields", and he maintains that no study so far has shown the efficacy of BCG. He also includes the British Medical Research Council's field study in his rejection of claimed results. In his criticism he seems to evade discussing the very significant meningitis-preventing action of BCG in that study. The last chapter deals with the use of chemoprophylaxis as a substitute for or adjuvant to BCG vaccination. In all, this volume seems to give a rather adequate information about the present controversial opinions and problems regarding BCG.

berto Hegglin: **Differentialdiagnose innerer Krankheiten.**

Georg Thieme Verlag, Stuttgart, 1957. 749 pages, 459 figures. Price DM 79.50.

The author, who is associate professor at the University of Zürich and head of the Internal Clinic of the St. Gallen Kantonenspital, published the first edition of this

book in 1952. The present volume is the 5th edition, which shows its great appreciation by students and graduate physicians. It stresses the correlation of organic functions. Physiologic-pathologic points of interest dominate. It has been the author's intention to deal with differential diagnostic problems of symptoms which the practitioner often meets and to tabulate them not from a specialistic but from a bed-side, working doctor's point of view. Perusal of the pages and reading some of the chapters testify that the author has succeeded in his task in a very satisfactory way. Although principally written for physicians occupying themselves with adult medicine, it contains much that is of clinical pediatric interest. Forty pages of general index facilitate the practical use of the volume, which can without reservation be recommended as an excellent differential-diagnostic reference book, especially for medical students and general practitioners.

Acta Pædiatrica **47**: 337—338. May 1958

ANNOUNCEMENTS

NAPT Commonwealth Chest Conference

This conference, incorporating the Annual Conference of the British Tuberculosis Association, will be held at the Royal Festival Hall, London, from July 1st to 4th, 1958. *Please address all correspondence to:* National Association for the Prevention of Tuberculosis, Tavistock House North, Tavistock Square, London, W.C. 1.

IX International Congress of Peadiatrics

The IX International Congress of Paediatrics will be held in Montreal, Canada, from July 19–25, 1959, under the auspices of the International Paediatric Association at the invitation of the Government of Canada and the Canadian Paediatric Society. The President is Professor Alan Ross, M.D., and the Secretary General, R. L. Denton, M.D. The scientific program has been planned to embrace the problems of child care in their broadest sense, and will include plenary sessions, panel discussions, original communications and scientific exhibits. Simultaneous interpretation will be employed for all plenary sessions. Official languages will be English, French and Spanish. A varied program of social events will be offered. Canada's bilingual metropolis is one of the cosmopolitan centres of North America and has many scientific, artistic, cultural and educational attractions, including two universities and two modern Children's Hospitals. The Laurentian Mountains and the St. Lawrence Seaway are both close to this charming city. The Preliminary Program and registration forms will be distributed in a few months time by the regional offices of the American Express Company.

The Sixteenth International Congress of the History of Medicine

This Congress will be held in Montpellier, France, September 22nd to September 28th, 1958. Professor Giraud is President and Dr. Louis Dulieu General Secretary. Correspondence should be sent to the General Secretary, c/o Faculté de Médecine, Montpellier, France.

Service d'Orientation

Le Conseil d'administration du Centre International de l'Enfance a pris la décision de créer un nouveau service, nommé Service d'Orientation. Ce Service aura pour tâche d'orienter et de guider le personnel médical et social s'occupant de l'Enfance, au cours de séjours, voyages de travail et visites faites par ce personnel hors de son propre pays. Le siège de ce Service sera placé dans les locaux du C.I.E., au Château de Longchamp, Bois de Boulogne. Paris 16.

The International Society of Hematology.

The Seventh Congress of the *International Society of Hematology* will be held in Rome at the Palazzo dei Congressi, EUR, September 7 to 13, 1958. The official languages of the Congress will be English, French, German, Italian and Spanish. Preliminary program: (1) Immunohematology; (2) Hemorrhagic Disorders; (3) Leukemia; (4) Anemia; (5) Nucleonics; (6) The Spleen and the Reticulo-Endothelial System.

For further information please write to: *Segreteria del VII Congresso Internazionale di Ematologia, Istituto di Patologia Medica, Policlinico Umberto I, ROMA (Italia).*

The Congress of the *International Society of Blood Transfusions* will be held at the same Palazzo dei Congressi, September 3 to 6.

The Twelfth Northern Pediatric Congress.

This Congress will be held in Helsingfors, June 29th to July 2nd 1958. Professor C. E. Räihä is President and Professor N. Hallman is General Secretary. Three main subjects will be discussed: *perinatal mortality and its prophylaxis, etiology of disorders of the urinary tract,* and *factors influencing the somatic development of children.* The address of the Organization Committee is Stensbäcksgatan 11, Helsingfors, Finland.

Acta Pædiatrica **47**: 339—349. July 1958

From the Department of Gynecology and Obstetrics, and the Wenner-Gren Cardiovascular Research Laboratory, Norrtull's Hospital, Stockholm, Karolinska Institutet, Sabbatsbergs Sjukhus, Stockholm, Sweden

A Technique for Perfusion of the Previable Human Fetus

by BJÖRN WESTIN, RUNE NYBERG and GÖRAN ENHÖRNING

When a previable fetus is kept at room temperature, the heart rate, systolic blood pressure, body temperature and oxygen tension of the blood rapidly decrease, while excessive amounts of carbon dioxide are accumulated in the blood. Changes in the ECG take place, implying ischemia of the heart. With few exceptions, these fetuses show no sign of life about 3–4 hours after birth (Fig. 1). When the fetus is kept at 37°C, the period of survival is considerably diminished, apparently due to higher metabolism and a limited store of oxygen, glucose, and other important nutritive elements (Enhörning & Westin, 1954; Westin, 1955).

It was demonstrated, however, that a single injection of oxygenated blood into the umbilical vein normalized the ECG, increased the blood pressure and improved the condition of the fetus in other ways. Therefore it seemed desirable to construct an apparatus by means of which it would be possible to perfuse the fetus continuously with oxygenated blood. Some preliminary perfusion experiments on previable human fetuses have been described previously (Enhörning & Westin, 1954). During these and several further experiments the main problem was how to prevent an increase of the blood volume within the fetus. Even a slight increase was found to cause hemorrhages and death of the fetus.

Two different methods for maintaining a constant fetal blood volume were applied without success: (1) control of the weight of the fetus, and (2) control of the inflow to and the outflow from the fetus by means of calibrated pumps.

That the first method was extremely difficult to use in practice can be clearly understood when one learns that the total blood volume of the fetus was only about 10 ml in some cases. Approximately one-third of the total blood volume must be pumped to and from the fetus each minute, and thus

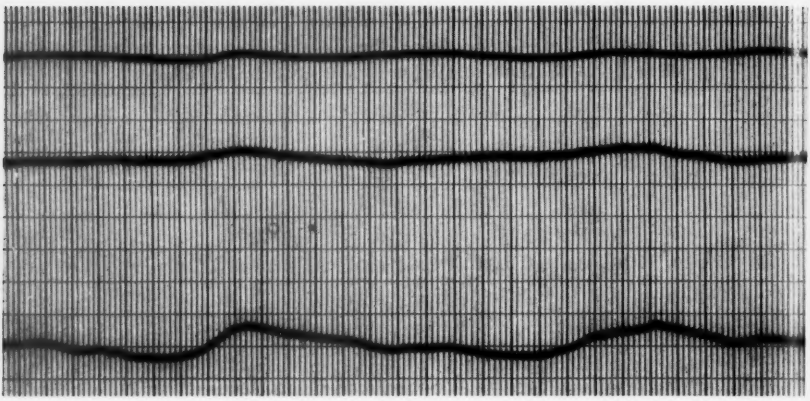


Fig. 1. Fetus, length 27 cm. Agonal ECG (lead I, II, IV) 4 hours after birth.

even a very small difference in capacity between the 2 pumps causes a considerable and progressive change of the fetal blood volume in some hours.

In the present paper a perfusion technique will be described, which makes it possible to keep the human fetus alive for several hours under conditions similar to those *in utero*.

The Perfusion Technique

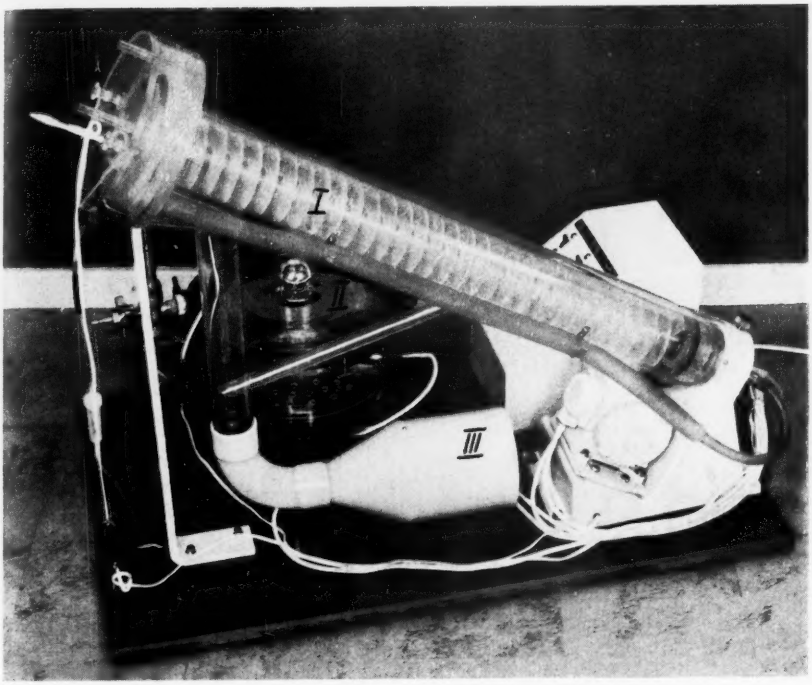
The Perfusion Apparatus

The perfusion apparatus (Fig. 2) consists of a perfusion chamber and an oxygenator. The perfusion chamber encloses the fetus and ensures a constant temperature and blood volume. The oxygenator serves the double purpose of oxygenating the blood and elevating it to a hydrostatic level suitable for the perfusion of the fetus.

The Perfusion Chamber

The perfusion chamber is a glass container filled with 5.5 per cent glucose, and may be tightly closed with a cover (Fig. 3). In the narrow lower part of the container is a thermo-regulated heating apparatus which ensures

Fig. 2. Photograph and schematic drawing of perfusion apparatus. I *The oxygenator.* 1, the spiral; 2, encasing cylinder; 3 and 4, inlets for the artery catheters; 5, thermometer; 6, oxygen inflow; 7, oxygen flow meter. II *Perfusion chamber.* 8, inlets with rubber stoppers; 9, thermometer; 10, thermo-regulated heating equipment; 11, perforated disc. III *Thermo-controlled heating equipment for the oxygenator.*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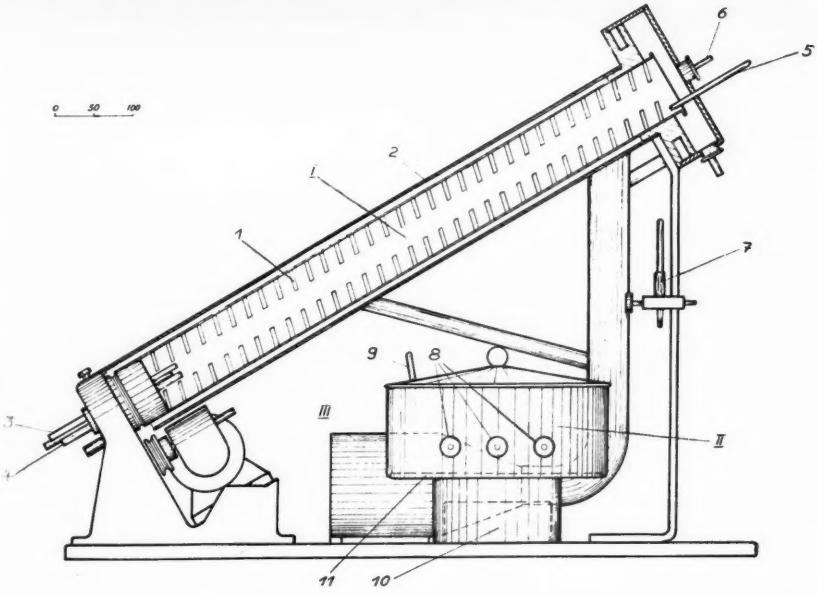
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Fig. 3. Perfusion chamber containing fetus.

a desired temperature between 25° and 38°C. When set at 37°C the temperature has not been found to go below 36.8° or above 37.2° in any part of the chamber. The heating time when the perfusion chamber is filled is about 50–60 minutes. Three holes in the wall of the container admit the catheters for perfusion and blood pressure recording and the cables of the ECG. The passage of the catheters through the rubber stoppers is facilitated by the arrangement shown in Fig. 4. When the catheters have been introduced into the umbilical vessels, the fetus is placed on a perforated disc above the heating apparatus. The perfusion chamber is then completely filled with isotonic glucose and closed with the cover. As all air is evacuated and the system closed, the volume of the fetus cannot change. Any volume injected into the umbilical vein will appear quantitatively in the outflow. The blood volume of the fetus will thus remain constant during the perfusion experi-

Fig. 4. Equipment for the passage of the catheters through the rubber stoppers without leakage.

ment. Depending on the flow rate the pressure within the perfusion chamber might vary a few mm Hg.

The Oxygenator

The parts of the oxygenator coming into contact with the blood are made of plexiglass, and the apparatus is easy to disjoint.[1]

The oxygenator consists of a cylinder with a spiral attached to its inner wall. The cylinder is placed at an angle of 30° to the horizontal plane and rotates with a speed of 28 r.p.m. The blood introduced into the lower part of the oxygenator from the umbilical artery catheters, is transported to the higher end in 69 seconds by the rotating cylinder with its inner spiral. The blood is simultaneously spread within the cylinder and the effective area available for oxygenation is about 4000 cm^2. Humidified oxygen passes in the opposite direction and the oxygen tension of the blood is thus gradually increased and the carbon dioxide decreased as the blood is transported to the upper end of the oxygenator. Here the blood is collected in a container

[1] The apparatus has been manufactured by Kifa, Stockholm, and sponsored by the "Association for the Aid of Crippled Children".

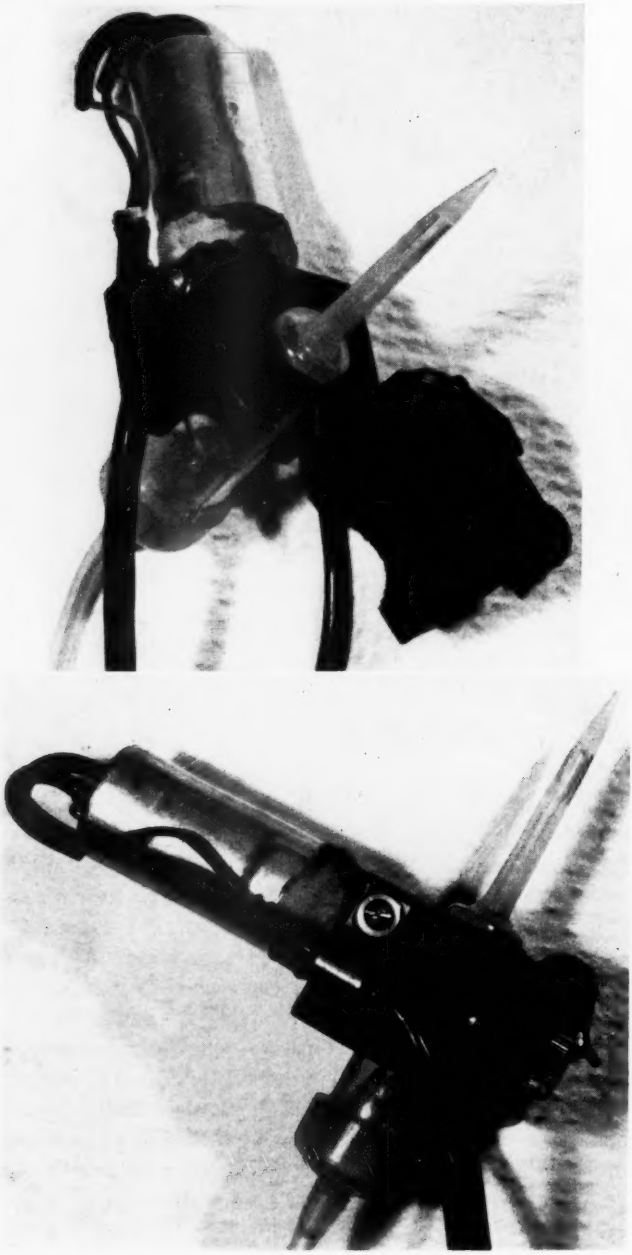

Fig. 5. Photocell drip counter.

with a capacity of 85 ml. Hardly any foam is formed. Via a catheter the blood passes through a filter to the umbilical vein of the fetus. The hydrostatic perfusion pressure is 40 cm water, whereas the hydrostatic pressure against the arteries is about 15 cm of water. The relation between the two pressures can be changed by altering the height of the perfusion chamber. The pump capacity of the oxygenator is 450 ml per minute. However, the optimal blood volume of the perfusion system is about 250 ml. The oxygenator then has a capacity of 100 ml per minute. This volume is not required by the fetus, but the blood surface in the container is kept at a constant level by backflow through an outer tube to the lower end of the cylinder. In general the pump function of the oxygenator is needed only intermittently. To ensure a constant temperature the oxygenator is encased in a larger cylinder and a thermo-regulated heating equipment blows warm air between the cylinders.

The oxygenator containing a blood volume of 250 ml has been tested at 37°C with an oxygen flow of 4 liters per minute. It then transported 100 ml blood per minute and the oxygen saturation of this blood increased from 45.4 to 97.4 per cent. The carbon dioxide content decreased from 52.3 to 35.5 per cent. In order to maintain the blood sugar level during the perfusion, glucose had to be added to the blood. During several hours of perfusion only negligible increases of plasma potassium concentrations were observed.

Incompatibility of blood groups must be taken into consideration. The fetal blood lacks agglutinins in its plasma. It would therefore be most adequate to use donor blood of group AB. Large quantities of blood belonging to this group were not available, and, as the red blood corpuscles of the fetus have a low titer of agglutinogen, the risk of giving another blood group is very small. Repeated controls have shown that there was no agglutination when group O (Rh-negative) was used for the perfusion. With heparin (5 mg per 100 ml blood) added to prevent coagulation, the blood was used shortly after being drawn from the donor.

The Recording Device

ECG, blood pressure and blood flow are recorded simultaneously on the same film by an Elema Triplex Electrocardiograph. The electrodes for ECG are introduced subcutaneously. For blood pressure recordings one arterial catheter is occasionally shifted to an Elema Electromanometer. Under the present experimental conditions the perfusion chamber containing the fetus functions as a valve pump. From this it follows that the hydrostatic pressure on the venous side does not influence the arterial pressure. The blood flow recorded on the film represents the flow when one umbilical artery

Fig. 6. Perfusion catheters cut for insertion.

is occluded. The blood flow is recorded by means of a photocell drip counter (Fig. 5) which can be applied to the drip chamber of blood transfusion sets in common usage. The error in the measurement of streaming velocity amounts to 5–10 per cent.

The Fetus

The fetuses were obtained from spontaneous and legally induced abortions.

The umbilical cord is clamped as soon as possible to prevent any change of the fetal blood volume during the delivery. The fetus is placed in the perfusion chamber, which is filled with 5.5 per cent glucose solution having a temperature of 25°C. In this way the body temperature of the fetus is rapidly reduced to that of the surrounding liquid, which is necessary in most cases in order to reduce the oxygen consumption of the fetus until the perfusion can be commenced.

About 3–5 cm from the umbilicus small incisions are made consecutively into the umbilical vessels. The insertion of the catheters into the umbilical vessels is facilitated by dilatation of the vessels with probes of different sizes. Soft plastic catheters (trade mark Pharmaseal, sizes 5–8) are then inserted into the umbilical arteries and the umbilical vein. In order to facilitate the insertion of the catheters and prevent occlusion of the outflow, the inserted ends of the catheters have been cut, as shown in Fig. 6.

When the 3 catheters have been introduced into the umbilical vessels, the tip of the catheter introduced into the umbilical vein reaches the caudal part of the ductus venosus Arantii, while the tips of the arterial catheters just reach inside the abdominal wall but can be introduced into the aorta. When the arterial outflow from the catheters functions, the positions of the catheters are secured by means of a ligature around the umbilical cord. The cover of the perfusion chamber is assembled and the container filled with isotonic glucose and then closed.

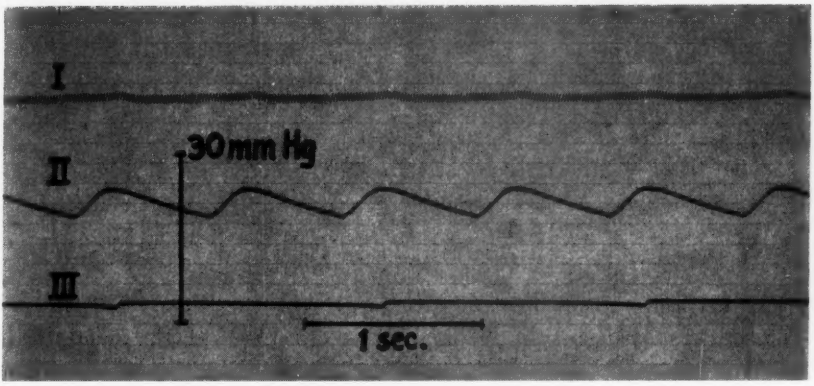

Fig. 7. Recording of I: ECG (lead I). II: arterial pressure (filter 3 = ≤ 6 p/s). III: drip flow, 11 hours after the perfusion was commenced. Weight of fetus: 100 g. Temperature: 30°. Arterial pressure 24 mm Hg. Heart rate: 80 per minute. Blood drip rate: 46 per minute (1.8 ml per minute).

Results

The results of perfusion experiments on 7 previable fetuses will be exemplified below. The period of survival, as shown by recordings of ECG, blood pressure, blood flow and determinations of the oxygen consumption of the fetus, has varied between 5 and 12 hours. Some fetuses have been perfused at a lowered body temperature for several hours, others at 37°C. No cold fits have been observed during the cooling or the warming of the fetuses.

During the perfusion experiments the fetuses performed movements of the head, body and limbs. These movements were vigorous, even at a temperature of 25°C. The fetal movements observed consisted of ventro- or dorsoflexion of the trunk, flexion or extension of the limbs and turnings of the head.[1] Swallowing and respiratory movements have not been observed under the present experimental conditions.

In fetuses weighing 200–375 g and recorded for several hours at 37°C the heart rate was approximately 120–180 per minute. The P-Q time was about 0.10 seconds and the arterial pressure 25–50 mm Hg.

In a male fetus (length 27 cm, weight 275 g, body temperature 37°C) the heart rate 6 hours after birth was 120, the P-Q time 0.10 seconds, the blood flow via both umbilical arteries 14.2 ml per minute and the arterial pressure 30 mm Hg. The oxygen tension in the umbilical vein and one artery was 95 and 44 mm Hg respectively. The experimentally obtained oxygen consumption of this fetus was 7.6 ml O_2 per k:lo per minute.

[1] A motion picture in color, illustrating the fetal movements described in this section, is available in the Department of Gynecology and Obstetrics, Sabbatsbergs sjukhus, Stockholm.

Five hours after birth a fetus weighing 100 g and recorded at 25°C showed the following properties: P-Q time 0.10 seconds, heart rate 96 per minute, arterial pressure 37 mm Hg, blood flow when one umbilical artery was occluded 2.7 ml per minute. The experimentally obtained oxygen consumption of this fetus at 25°C was 1.0 ml per kilo per minute. In Fig. 7 a record is shown of this fetus 11 hours after birth at a body temperature of 30°C.

Discussion

The perfusion apparatus described in this paper has several advantages. The construction is simple, the oxygenator effective, and the apparatus is easy to disjoint and clean. The double function of the oxygenator eliminates the use of circulation pumps which traumatize the blood. The oxygenating capacity can be considerably altered by changing the amount of blood in the oxygenator and the rotation speed of the spiral. The simple principle of the perfusion chamber has solved the problem of keeping the small blood volume of the fetus constant.

It may be of some interest to compare the results exemplified in the present paper with some previous investigations of prenatal life.

Our determinations of the blood pressure and oxygen consumption of the human previable fetus at 37°C are in agreement with those made by Barcroft (1947) on sheep fetuses. The comparatively large oxygen consumption of the perfused previable human fetus is also in accordance with approximate determinations of the oxygenation of the intrauterine human fetus by means of hystero-photography (Westin, 1957).

The recordings of the oxygen consumption of the hypothermic fetus are in agreement with the basic experimental work on hypothermia by Bigelow *et al.* (1950).

The perfusion technique here presented offers new possiblilities of extending our knowledge of the physiology of the human fetus. It also appears possible that the technique may be used in the future treatment of premature and asphyxiated newborn infants.

Summary

A perfusion technique of the previable human fetus is described in detail. The fetuses survived 5–12 hours. ECG, blood pressure, and blood flow were recorded simultaneously. Examples of the oxygen consumption of hypo- and normo-thermic fetuses are presented.

Description d'une technique de perfusion du fœtus humain préviable.

Description détaillée d'une technique de perfusion du fœtus humain préviable. Les fœtus survécurent de 5 à 12 heures. L'ECG, la pression artérielle et le débit sanguin furent enregistrés simultanément. Il est cité des exemples de la consommation d'oxygène de fœtus hypothermiques et normothermiques.

Beschreibung einer Perfusionstechnik für den noch nicht lebensfähigen menschlichen Foetus.

Eine Perfusionstechnik für den noch nicht lebensfähigen menschlichen Foetus wird ausführlich beschrieben. Die Foeten blieben 5–12 Stunden am Leben. EKG, Blutdruck und Blutströmungsgeschwindigkeit wurden gleichzeitig registriert. Beispiele von Sauerstoffverbrauch von hypo- und normothermischen Foeten werden angeführt.

Descripción de una técnica de perfusión en el feto humano previable.

Descripción detallada de una técnica de perfusión en el feto humano previable. Los fetos sobrevivieron durante 5 a 12 horas. El ECG, la presión y la circulación sanguínea, fueron registrados simultáneamente. Exposición de ejemplos del consumo de oxígeno en fetos hipo- y normotérmicos.

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On the Influence of Uterine Contractions on the Blood Pressure in the Umbilical Vein at Birth

by RUNE NYBERG and BJÖRN WESTIN

Immediately after birth a transfer of placental blood takes place through the vein to the newborn infant. Opinions about the cause of this transfer have varied. Ribemont (1879) considered that the transfer was effected as a result of the onset of respiration. Haselhorst (1929) stated that the uterine contractions after delivery played an important role in this transfer. Hörmann & Lemtis (1954) considered that the contraction of the placental and umbilical vessels was the most important factor.

Haselhorst (1929) measured the venous pressure on the placental side of a ligature on the cord. He found that the pressure increased from 47 to 123 mm Hg during the uterine contractions. In another investigation he recorded the venous pressure in the cord with the circulation intact. With this method the mean pressure between the contractions was much lower and it was hardly influenced by the uterine contractions.

During some experiments concerning fetal anoxia due to partial obstruction of the umbilical cord, we compressed the cord with a pressure a little lower than that of the umbilical artery. The compression was performed by means of a special pneumatic rubber cuff. In spite of this venous obstruction the newborn infant *gained* in weight. It was therefore assumed that the venous pressure at least temporarily surmounted that of the arteries

Material and Method

The blood pressure in the umbilical vein was measured in 17 normal births. The mothers received a slight chloroform analgesia (3–5 g) at the delivery of the fetal head. The babies who weighed 2900–4200 g were not asphyxiated. Within 30 sec. after birth a soft plastic tube was inserted into the vein near vulva with the point towards placenta. The outer dia meter

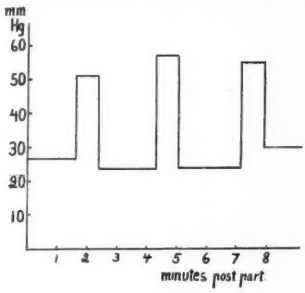

Fig. 1. Mean values of the lowest and the highest pressures in the umbilical vein.

of the catheter was 1.0 mm. The pressure was recorded by an Elema electromanometer (Filter 2). The uterine contractions were easily recorded by gently palpating the uterus and there was never any uncertainty about the uterine tonus conditions.

Results

On an average the uterine contractions came after about 2, 4.5 and 7.5 minutes respectively. Each contraction lasted about 40 sec. The placenta was separated within about 8 minutes after birth.

The mean values of the lowest venous pressures between and the highest during the uterine contractions are indicated in Fig. 1.

Between the uterine contractions we could not find any considerable variations in the venous pressure, other than those which were induced by the infant's cries. The maximal variation registered was 10 mm Hg, but generally the fluctuations were 2–5 mm Hg.

After the separation of the placenta the venous pressure remains constant on about 30 mm Hg until the delivery of the placenta.

The pressure during the uterine contractions could reach considerable heights. An example is given in Fig. 2. The highest and the lowest venous pressure during a contraction were 115 and 24 mm Hg respectively.

Discussion

The relatively high pressure in the umbilical vein is inconsistent with the old theory of suction as the only cause of the transfer of blood to the newborn infant.

The well limited and palpable uterine contractions were synchronous with the highest pressures recorded in each case. Hörmann & Lemtis (1954) could not credit the uterine contractions with the transfer of blood from

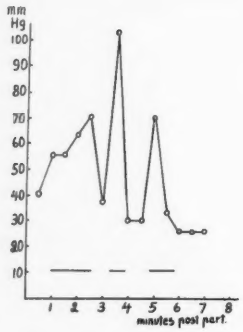

Fig. 2. Variation of the venous pressure in a single case. —— = uterine contraction.

the placenta but considered this transfer to be due to contraction waves over all the umbilico-placental vascular system.

According to our investigation there was no other considerable cause of the increase of the venous pressure than the uterine contractions.

From our work it follows that the uterine contraction is the most important factor in the postnatal transfusion of blood to the infant.

Summary

The pressure relations in the umbilical vein were studied in 17 infants immediately after delivery.

It was found that the uterine contractions was the most important factor in the postnatal blood transfusion to the infant.

Influence des contractions utérines sur la pression artérielle de la veine ombilicale à la naissance.

Le mécanisme de la pression de la veine ombilicale fut étudié chez 17 nourrissons tout de suite après l'accouchement. On découvrit que les contractions utérines étaient le facteur le plus important de la transfusion post-natale de sang au nouveau-né.

Über den Einfluss der Gebärmutterkontraktionen auf den Blutdruck in der Nabelvene zur Zeit der Geburt.

Die Druckverhältnisse in der Nabelvene unmittelbar nach der Entbindung wurden bei 17 neugeborenen Kindern studiert. Es zeigte sich, dass die Uteruskontraktionen den bedeutendsten Faktor für die Bluttransfusion zum Kind in der postnatalen Periode darstellt.

De la influencia de las contracciones uterinas en la presión sanguínea de la vena umbilical durante el parto.

Estudio de las inferencias relativas a la presión existente en la vena umbilical en 17 niños inmediatamente después del parto. Se deduce que las contracciones uterinas constituyen el factor de mayor importancia en la transfusión de sangre postnatal al neonato.

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On the Amount of Gastric Contents in the Normal and the Asphyxiated Newborn Infant

by BJÖRN WESTIN

In the *asphyxiated* newborn infant it has been assumed that excessive amounts of amniotic fluid are ingested *at* or *prior to* delivery. This fluid might later be regurgitated and aspirated, thus initiating respiratory distress of the newborn infant (Gellis, White & Pfeffer, 1949). Suction of the gastric contents has later been employed as a technique for the prevention of asphyxia in the newborn infant (Little, D'Andrea & Mastrangelo, 1951). In 225 cesarean sections no gastric aspiration was employed and the corrected fetal mortality was 4.4 per cent. In 179 following cesarean sections gastric aspiration was used and the corrected fetal mortality was 2.8 per cent. The authors drew the conclusion that the fetal mortality was lowered by approximately 50 per cent. However, when the present author calculated the standard error of the difference between the two groups of Little, D'Andrea & Mastrangelo (1951), no significant difference was found ($D < \varepsilon$).

It was therefore considered of some interest to measure the amount of gastric contents in the normal and in the asphyxiated newborn infant in order to find out if this amount was perceptibly increased in asphyxia.

Material and Method

The pregnant women received nitrous oxide analgesia (*Sedator* apparatus, *Aga* Ltd.) during labor and when the head of the fetus had to be delivered, chloroform analgesia was administered. Immediately after birth a urethral catheter was passed gently into the stomach and the fluid aspirated by means of a 5 ml syringe. The technique was similar to that of Little, D'Andrea & Mastrangelo (1951).

Results and Discussion

In normal deliveries the fluid obtained was viscid containing caseous material. In some cases, when intrauterine asphyxia had occurred, the fluid was stained green.

In 229 normal deliveries (no signs of asphyxia prior to or after delivery) the mean amount of gastric fluid was 3.2 ± 0.2 (ε) ml. In 6 low-forceps deliveries (no signs of asphyxia prior to or after delivery) the mean amount obtained was 2.4 ± 1.3 ml.

In 12 spontaneously delivered asphyxiated infants the mean value was 4.8 ± 1.1 ml, while the corresponding figure for 15 asphyxiated infants delivered by mid-high or low forceps was 3.1 ± 2.0 ml. The differences between the different groups were insignificant.

The present results seem to indicate that no perceptible change occurred in the amount of gastric fluid measured when the fetus was asphyxiated. If the unchanged volume depended on the fact that part of it had been aspirated by the lungs prior to the delivery or in a more rapid passage to the bowels, the respiratory distress of the newborn does not seem to be improved by the suction of a small amount of gastric fluid.

Summary

The amount of gastric contents was measured in the normal and in the asphyxiated newborn infant. No significant difference was found.

Quantité du contenu de l'estomac du nouveau-né normal et asphyxié.

La quantité du contenu de l'estomac fut mesurée chez le nouveau-né normal et asphyxié, sans que l'on remarquât de différence significative.

Über den Betrag von Mageninhalt beim normalen und asphyktischen neugeborenen Kinde.

Der Betrag von Mageninhalt wurde beim normalen und beim asphyktischen Neugeborenen bestimmt. Kein wesentlicher Unterschied wurde festgestellt.

Del contenido gástrico total en el recién nacido normal y en el asfixiado.

Medición del contenido gástrico total del recién nacido normal y del asfixiado. No se encuentra diferencia significativa.

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The Arterial Blood Pressure of the Newborn Infant

Part I. The Blood Pressure in the Umbilical Artery of the Mature Normal Newborn Infant

by RUNE NYBERG and BJÖRN WESTIN

The arterial blood pressure of the newborn infant has been recorded by the following investigators:

Ribemont (1879) obtained an average value of 63.7 mm Hg in the umbilical artery. No data were given on the pulse amplitude.

Haselhorst (1929) found a mean pressure of 75 mm Hg (62–110) in 8 normal deliveries and 68 mm Hg in one cesarean section. He punctured the vessel and used a mercury manometer (no data on the pulse amplitude).

Woodbury, Robinow & Hamilton (1938) related the pressure of the brachial artery recorded with a cuff to the pressure measured directly in the umbilical artery with a photographic manometer. Only with a cuff of 2.5 cm width was agreement obtained between the two methods. The mean value from 24 normal deliveries was 80.1/46.3 mm Hg. Anesthesia to the mother had no effect. Nor did the onset of respiration cause any permanent change in the pressure.

This study was undertaken in order to (1) ascertain the normal arterial pressure curve of mature newborn infants, and (2) demonstrate the possible influence of respiration on the arterial blood pressure.

In a subsequent paper the arterial blood pressure of asphyxiated infants will be presented.

Material and Method

We have examined 20 mature normal newborn infants having a mean weight of 3528 g (range 2630–4160). Onset of respiration was spontaneous in every case after a mean time of 19 sec (range 0–90).

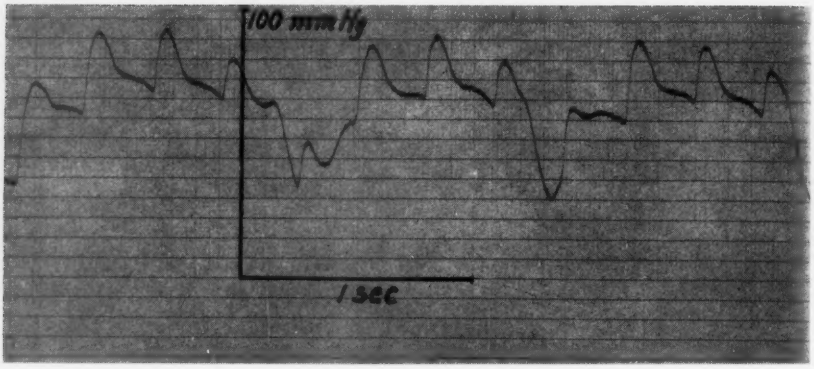

Fig. 1. Blood pressure curve from the umbilical artery 32 sec after birth demonstrating the effect of respiration.

One umbilical artery was punctured at a distance of 3 cm from the umbilicus and the point of the needle was directed towards the infant and inserted 2–3 cm. The puncture was performed at a mean time of 16 sec (range 6–60) after birth. The needle having a calibre of 1.0 mm was already attached to an Elema electromanometer (Filter 2 $\leq$ 12 p/s). The placenta was not separated during the recordings.

During the delivery of the fetal head the mothers received a slight chloroform analgesia (3–5 g chloroform).

Results and Discussion

The measuring of the systolic and diastolic pressures on the film record was not without difficulties because of the great influence of the thoracic movements on the pulse curve. This influence could bring about a difference of 70 mm Hg between the highest and lowest systolic pressure in the same infant. The mean value of the highest respiratory differences in all cases was 38 mm Hg (range 14–70). An example of this respiratory influence is shown in Fig. 1. This variation was quite pronounced even before the first cry.

If the pressure was measured when the curve was horizontal as in Fig. 2 the mean value of the blood pressure in the 20 infants was 87.8 $\pm$ 3.0/54.5 $\pm$ 2.7 mm Hg. This value was recorded at a mean time of 18 sec after birth (range 8–70).

There was no obvious permanent alteration of the pressure in connection with the onset of respiration.

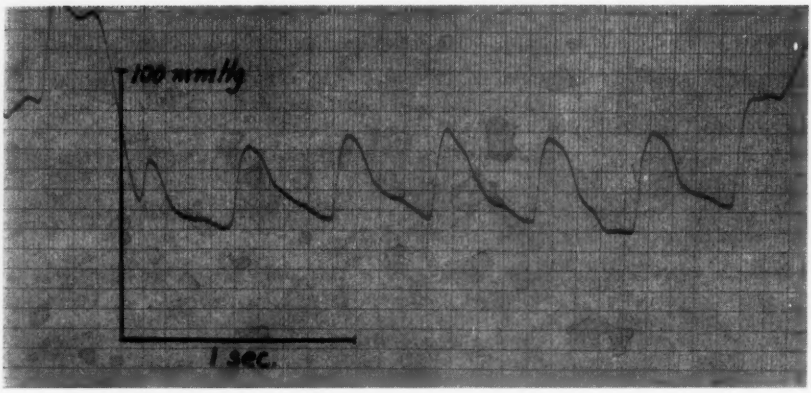

Fig. 2. Blood pressure during a long interval between two respirations 6 sec after birth.

Our figures for the mean pressure are somewhat higher than those recorded by previous investigators. But according to our results in may be difficult to check the real pressure because of the big alterations produced by the thoracic movements.

Summary

The blood pressure in the umbilical artery was recorded in 20 mature normal newborn infants immediately after birth by an electromanometer. The thoracic movements caused considerable variations in the pressure recorded. The mean pressure was 87.8 ± 3.0/54.5 ± 2.7 mm Hg.

La pression artérielle du nouveau-né.
I. *La pression de l'artère ombilicale du nouveau-né normal à terme.*

On mesura, à l'électromanomètre, la pression de l'artère ombilicale de 20 nouveaux-nés normaux nés à terme tout de suite après la naissance. Les mouvements thoraciques causèrent des variations importantes de la pression enregistrée. La pression moyenne fut de 87,8 ± 3,0/54,5 ± 2,7 mm de mercure.

Der arterielle Blutdruck beim neugeborenen Kind.
I. *Der Blutdruck in der Nabelarterie des normalen, vollreifen Neugeborenen.*

Der Blutdruck in der Nabelarterie wurde bei 20 vollreifen normalen neugeborenen Kindern unmittelbar nach der Geburt mit Hilfe eines Elektromanometers bestimmt. Die Bewegungen des Brustkorbs verursachten wesentliche Schwankungen in dem aufgezeichneten Druck. Der durchschnittliche Blutdruck betrug 87,8 ± 3,0/54,5 ± 2,7 mm Hg.

De la presión sanguínea arterial en el recién nacido.
I. *La presión sanguínea en la arteria umbilical del neonato normal nacido a término*

La presión sanguínea en la arteria umbilical de 20 neonatos normales nacidos a término, ha sido registrada inmediatamente después de nacer, mediante un electromanómetro. Los movimientos torácicos determinaron variaciones considerables en las presiones registradas. Presión media: 87,8 ± 3,0/54,5 ± 2,7 mm mercurio.

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Some Aspects of the Use of Arterial Heparin Blood in the Treatment of Asphyxiated Newborn Infants

by BJÖRN WESTIN

In a previous paper (Enhörning & Westin, 1951) a method of treating asphyxiated newborn infants was described. This method aimed at treating shock and hypoxemia by giving a transfusion of oxygenated blood to the newborn infant.

In a subsequent investigation (Enhörning & Westin, 1954) the effect of such transfusions was studied on previable human fetuses. It was found that in asphyxiated fetuses citrate blood had a deleterious effect on heart activity, partly due to hypocalcemia. Oxygenated heparin blood on the other hand was capable of restoring heart activity and blood pressure even in very advanced stages of asphyxia.

In order to get some information on the possiblility of using arterial heparin blood as a method of routine in the treatment of asphyxiated newborn infants, this subject was studied in the present investigation. Of special interest in this connection was a possible increase in carbon dioxide tension and a leakage of potassium from blood cells which might limit the period of storage. By using hydrophobic glass bottles this latter process might be partly prevented.

The oxygen-binding capacity of stored venous citrate and heparin blood was found to be practically unchanged for several weeks (Mittelstrass, 1939; Fischer & Schürch, 1941). The leakage of potassium from erythrocytes to plasma in ordinary glass bottles was recently studied by Schwalm (1952) who found a rapid increase from 4.1–4.6 to 10.3 m.eq./l during the first ten days.

The average serum concentration of potassium was found to be significantly higher in newborn infants (7.8 m.eq./l) than in adults (McCance & Young, 1941).

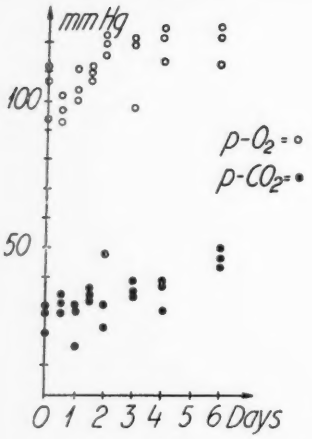

Fig. 1. The oxygen and carbon dioxide tension of blood stored in siliconized glass bottles.

Materials and Methods

The donor blood was obtained by puncturing one brachial artery of a healthy adult under local anesthesia. The transfusion unit was connected with the arterial canula by means of a nylon tube. The donor blood was collected in 3 transfusion units, each containing 80 cc of blood and 5 mg heparin in 20 cc och 5 per cent glucose solution. In each bottle the air content was approximately 25 cc at atmospheric pressure. The transfusion bottles (manufactured by Vitrum Ltd.) were coated with silicone and sealed with a rubber membrane. The blood was stored at 2–4°C. Blood samples were drawn after different periods of time. Before blood samples were taken, sedimentation was prevented by occasional shaking.

Oxygen and carbon dioxide tensions were determined according to a method described by Björk & Hilty (1954). Duplicate determinations showed a method error of 2 per cent. Hemolysis in plasma was determined according to Hunter (1951). Potassium in plasma was determined by internal standard flame photometry. The method error was 1 per cent.

Results

Preliminary investigations indicated that 5 mg of heparin was necessary to prevent clotting for one week in the transfusion unit described. In Fig. 1 determinations of oxygen and carbon dioxide tensions are collected. The increase of oxygen tension during the time of observation was insignificant, while carbon dioxide tension increased significantly. The mean value on the first day was 25 ± 3 mm Hg and on the sixth day 45 ± 3 mm Hg.

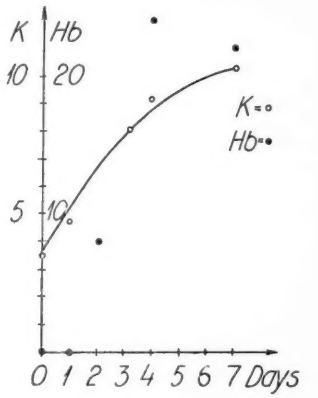

Fig. 2. The leakage of potassium (o = m. eq/l) and the hemolysis (• = mg Hb/100 ml plasma) of blood stored in siliconized glass bottles.

The rate of hemolysis and leakage of potassium from blood cells to plasma are indicated in Fig. 2. The hemolysis was inconsiderable but seemed to parallel the increase of potassium in plasma. These results are in agreement with the results obtained by Schwalm (1952) using ordinary glass bottles.

Discussion

From the results presented above it seems clear that the possibility of using arterial heparin blood in the treatment of asphyxiated newborn infants must be limited to the first few days. The moderate accumulation of carbon dioxide in the blood during the first week does not interdict its use. The accumulation of potassium in plasma on the other hand limits the period of storage to four days, if the potassium concentration should be kept within the normal range for newborn infants. This seems to be of importance when reviving asphyxiated newborn fetuses.

The present data on potassium leakage in siliconized glass bottles are not more favorable than those presented by Schwalm (1952).

When using arterial heparin blood in treating asphyxiated newborn infants a corresponding amount of protamine hydrochloride should be given intravenously immediately after the transfusion.

Summary

Some aspects of the use of arterial heparin blood in the treatment of asphyxiated newborn infants are discussed with special reference to the time of storage of the blood.

Quelques aspects de l'emploi du sang hépariné artériel dans le traitement de l'asphyxie du nouveau-né.

L'auteur étudie quelques aspects de l'emploi du sang hépariné artériel dans le traitement de l'asphyxie du nouveau-né, avec mention particulière de la durée de préservation du sang.

Gewisse Gesichtspunkte für die Anwendung von heparinisiertem, arteriellem Blut bei der Behandlung von asphyktischen Neugeborenen.

Gewisse Gesichtspunkte für den Gebrauch von heparinisiertem, arteriellem Blut bei der Behandlung von neugeborenen Kindern mit Asphyxie werden dargelegt mit besonderer Berücksichtigung der Zeit der Blutaufspeicherung.

Algunos aspectos del uso de sangre heparina arterial en el tratamiento de los recién nacidos asfixiados.

Presentación de algunos aspectos del uso de sangre heparina arterial en el tratamiento de los recién nacidos, especialmente con referencia al tiempo de acumulación de la sangre

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Hospital Outbreak of Adenovirus Type 3 Infections

A Clinical and Virologic Study on 38 Patients Partly Involved in a Nosocomial Outbreak

by JAN BARR, LARS KJELLÉN and ARNE SVEDMYR

In the summer and fall of 1955 an epidemic of pharyngoconjunctival fever (1), caused by adenovirus type 3, occurred in the middle of Sweden. It apparently started in the two communities of Kumla and Frövi in the middle of July. These outbreaks have been analyzed previously (3). During the following months the epidemic reached the town of Örebro (70,000 pop.) located 20 kilometers north and south respectively of the afore-mentioned communities.

This paper is primarily concerned with the variations in clinical pictures, observed by one of us (J. B.) among patients infected with adenovirus type 3, as well as with the spread of the infection inside the hospital.

Three groups of patients will be described: 9 patients directly admitted to the hospital for infectious diseases in Örebro (2 of them from Kumla), 11 cases secondary to these and observed as outpatients and, finally, 18 patients involved in an outbreak within the hospital.

Virus Isolations and Serological Tests

Stools and paired sera and to a certain extent also conjunctival and nasopharyngeal specimens were collected.

Isolation of virus and assay of complement-fixing and neutralizing antibodies against adenoviruses were performed according to methods outlined elsewhere (2).

Results of Clinical and Laboratory Investigations

I. Cases Admitted Directly to the Hospital

These 9 patients (No. 1–6, 13, 18 and 23, Figs. 1–4) were children aged from 2 to 12 years. Naturally, these cases were clinically the most pronounced. The first two patients, Cases 1 and 2, were referred in August 1955 from Kumla for diagnosis, since the local doctors had observed an epidemic of a clinically well delimitable, highly contagious disease with fever, sore throat, conjunctivitis and diarrhea as its most prominent symptoms. With the exception of gastrointestinal symptoms the clinical picture exhibited great similarities to the "pharyngoconjunctival fever", described by Bell *et al.* (1). When it became evident from the epidemiologic field investigations (3) that the Kumla–Frövi epidemic was also caused by adenovirus type 3, the previously frozen specimens from our patients were sent to the Virus Department of the Central Bacteriological Laboratory of Stockholm. In both patients (No. 1 and 2) adenovirus type 3 was isolated from the faeces and, in one of them, high titers of complement-fixing and type-specific neutralizing antibodies were demonstrated.

Attention having been directed to the clinical picture, 7 more type 3 infections were demonstrated among referred patients and 11 infections among contacts with these in the town of Örebro. The diagnosis was suspected in these later hospital cases because of a more or less typical clinical picture and was verified, with one exception (No. 23), through the isolation of type 3 adenovirus (mainly from faeces; in some cases also from the conjunctiva, nose and pharynx) together with a 4-fold increase in complement-fixing antibodies or, when only one serum specimen was obtained, CF-titers of ≥ 16. In the two cases (No. 3 and 18) where titration in paired sera of neutralizing antibodies against adenovirus type 3 was performed, it showed a definite rise. One case (No. 23) was included although no specimen was available for virus isolation since the clinical picture was unequivocal, the titers of complement-fixing and neutralizing antibodies in convalescent serum were high, and the same clinical picture developed in contacts.

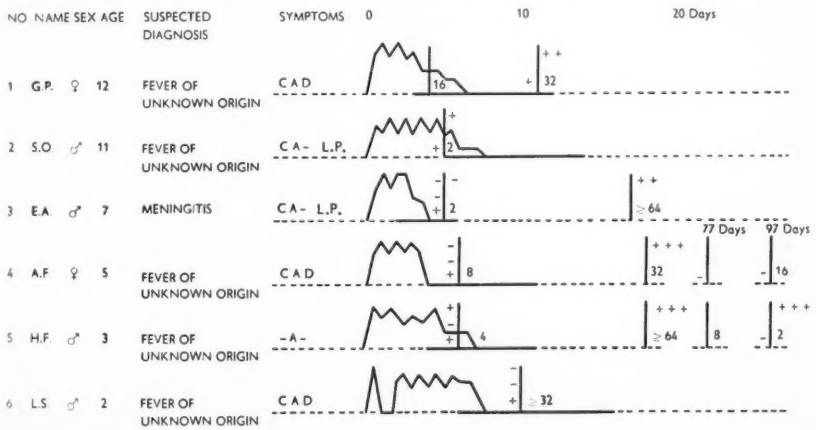
The diagnosis of referring doctors were extremely varying and included fever of unknown origin in 5 cases, suspected meningitis in 2 cases, suspected diphtheria (No. 23) and peripheral facial paralysis in 1 case each. It should be pointed out in this connection that in two siblings with symptoms indistinguishable from those in the verified cases, neither virus nor complement-fixing antibodies could be demonstrated.

The two original patients (No. 1 and 2) were investigated more thoroughly from the etiologic point of view. In both cases attempts at virus isolation in suckling mice gave negative results. Paired sera were examined for the presence of complement-fixing

antibodies against herpes simplex, mumps, toxoplasmosis and influenza A and B with negative results. Dye test according to Sabin was negative. Specific agglutinating or lytic antibodies could not be demonstrated against eight leptospira strains. (All these tests were performed at the Virus Laboratory, Sahlgrenska Sjukhuset, Gothenburg.) Bacteriologic investigation of specimens from the nose and pharynx showed growth in one case of *Staphylococcus aureus* and *Escherichia coli*, in the other case of *Haemophilus influenzae* of undetermined type. (These and the following tests were performed at the State Bacteriological Laboratory, Stockholm.) Stool cultures for *Salmonella* and *Shigella* bacteria were negative, as were agglutination tests against *Salmonella typhosa* and *paratyphi* A, B, C and D, *Brucella abortus* and *Pasteurella tularensis*.

The clinical symptoms in those cases admitted directly to the Hospital are shown in Figs. 1–5 and the explanatory text accompanying Figs. 1 and

FIG. 1. Patients directly admitted to the hospital.
(For abbreviations and symbols see explanatory text, Fig. 4.)



Case No. 3. EA. Jr. No. 49 03 21: A seven-year-old, previously healthy boy became acutely ill two days prior to admission with pains in the back of the neck, headache and fever that remained between 39° and 40°C. In addition he had such severe pain in both legs that he had to be supported in order to be able to walk. There were no gastrointestinal symptoms. The doctor called in also found a certain stiffness of the neck and referred the patient as suspected meningitis.

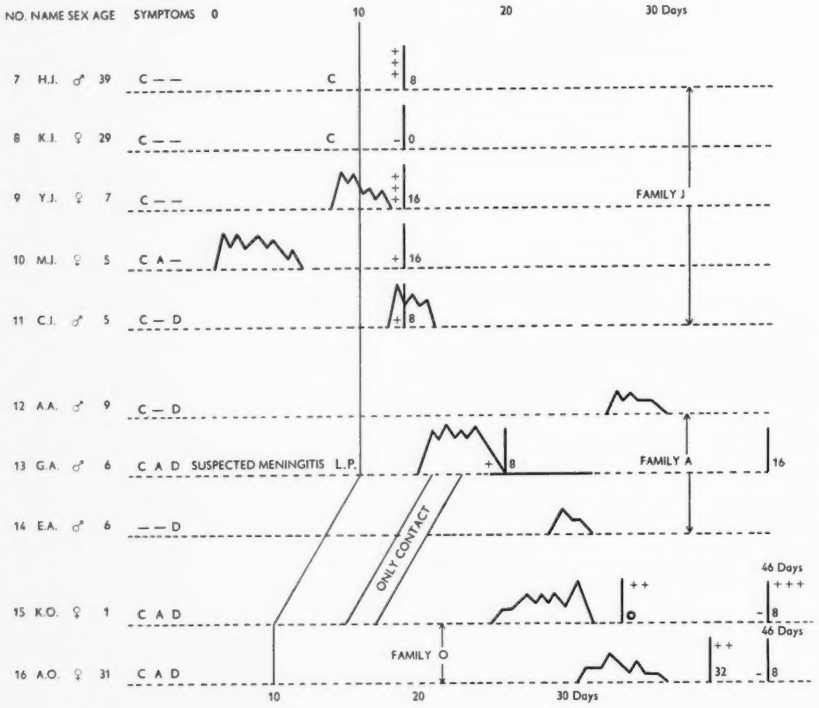
Examination on admission showed a slightly affected boy with 40.1°C temperature. The pharynx was slightly congested and reddened. There were abundant small glands apparent on the neck, in the axillae and groins. The conjunctivae were slightly reddened bilaterally. The neurologic status was normal with the exception of positive Lasègue's and Kernig's signs at 70° bilaterally. There was no paralysis, no definite stiff neck. Lumbar puncture gave clear colourless fluid with 2 cells/mm³. Quantitative protein was 13 mg/100 ml. Mastic test was negative.

The patient became fever-free in 3 days, but had slight pains in the back of the neck the first days. At follow-up examination 14 days later he was completely symptom-free except for slight residual irritation of the conjunctivae and slight general lymphadenopathy.

Adenovirus type 3 was isolated from faeces but not from conjunctival and pharyngeal specimens taken at admission. Neutralizing antibodies in paired sera showed a rise from 0 to + + and complement-fixing antibodies from 2 to ≥ 64.

FIG. 2. Familial infections (Families J, A and O).

Families J and A neighbours, their children playmates. Child K. O. (No. 15) only contact between families A and O during two days. (For abbreviations and symbols see explanatory text, Fig. 4.)


NO. NAME SEX AGE SYMPTOMS 0
10
20
30 Days
7 H.J. ♂ 39 C — —
8 K.J. ♀ 29 C — —
9 Y.J. ♀ 7 C — —
10 M.J. ♀ 5 C A —
11 C.J. ♂ 5 C — D
12 A.A. ♂ 9 C — D
13 G.A. ♂ 6 C A D SUSPECTED MENINGITIS L.P.
14 E.A. ♂ 6 — — D
15 K.O. ♀ 1 C A D
16 A.O. ♀ 31 C A D
FAMILY J
FAMILY A
FAMILY O
ONLY CONTACT
46 Days
46 Days
10
20
30 Days

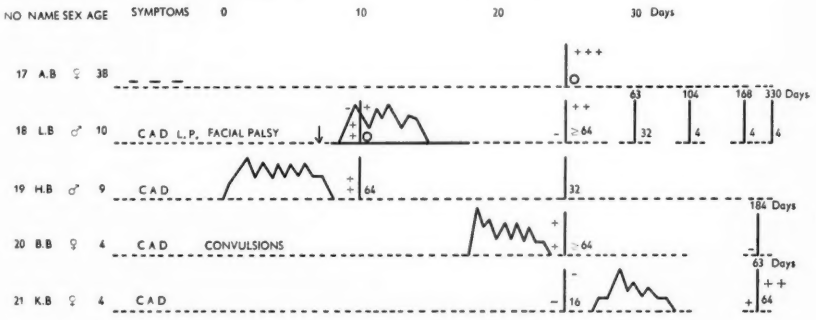
3. As may be seen from Fig. 5, fever, pharyngitis, conjunctivitis and moderate general lymphadenopathy dominated. In addition, analoguos with the Kumla epidemic (3) but contrary to epidemics described earlier (1), diarrhea and other gastrointestinal symptoms were common.

Among the individual symptoms the *fever*, as may be seen from the different figures, usually had a rapid onset, continued high and spontaneously dropped by lysis after a few days. The duration of the fever varied between five and eight days with a mean duration of six days. The maximum temperature varied between 39,2 and 40,1°C.

All but one of these hospitalized patients showed evidence of *conjunctivitis*, although in two cases only unilateral. In the pronounced cases the conjunctivitis was of pseudomembranous type with congestion of both palpebral and ocular conjunctiva, moderate follicular swelling of the conjunctival

FIG. 3. Familial infections (Family B).

(For abbreviations and symbols see explanatory text, Fig. 4.)



Case No. 18. LB. Jr. No. 45 08 17: This was a ten-year-old girl with a certain predisposition to upper respiratory tract infections, frequently in combination with otitis. Thus she had fever lasting one week with slight pains in the left ear five weeks before the onset of the present disease. On Oct. 20, 1955, the patient awoke with left-sided facial paralysis involving all three branches, without other concurrent symptoms. She was admitted the following day to the Hospital for etiologic investigation.

Examination on admission revealed nothing pathologic other than the facial paralysis. The day after admission she had a temperature of 40°C, pharyngitis, unilateral conjunctivitis with exsudate, general lymphadenopathy and, on the third day, frequent diarrhea, which continued for 48 hours. There were no other neurologic symptoms. Lumbar puncture gave clear, colourless fluid with 1 cell/mm³. Quantitative protein was 18 mg/100 ml. Mastic test was negative.

The subsequent course was entirely free from complications and the facial paralysis successively subsided completely.

Complement fixation against poliovirus (4) in paired sera was negative for all three types. Repeated tests for salmonella in faeces were negative. Adenovirus type 3 was demonstrated at the time of admission in specimens from the pharynx and in faeces, but not in conjunctival samples. Neutralizing antibodies in paired sera showed a rise from + to + + and complement-fixing antibodies from < 2 to $\geqslant 64$.

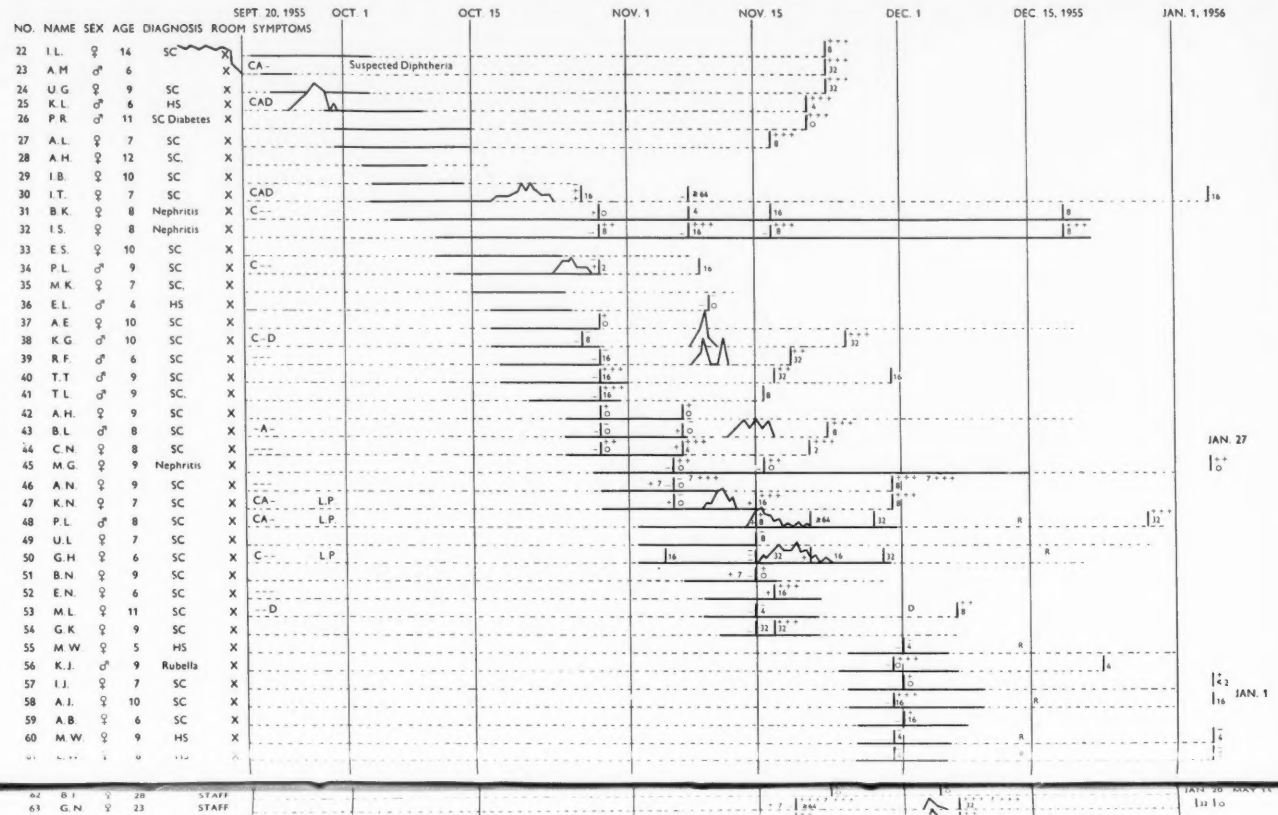
As may be seen above, all four children in this family were infected with adenovirus type 3. The mother had no symptoms but + + + type-specific neutralizing antibodies were demonstrated in her serum. The father had concurrently conjunctivitis, nausea and fever, but no specimens for virus diagnosis were obtained.

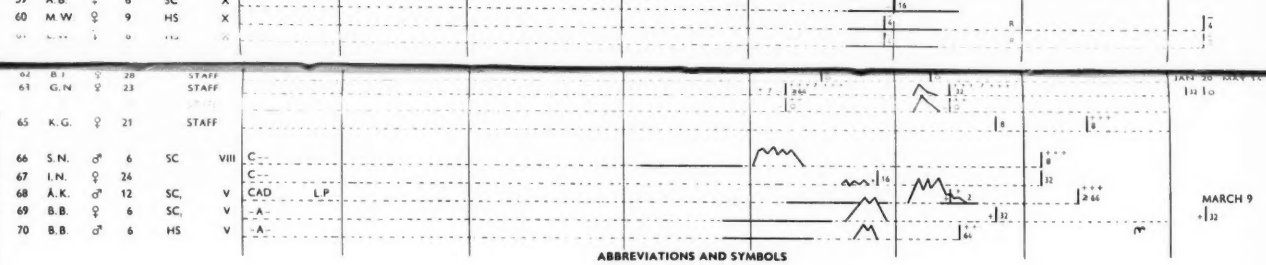
Although adenovirus type 3 was demonstrated in a few cases in the present material before typical clinical signs of infection appeared, the facial paralysis in this case was interpreted as a chance occurrence without etiologic relation to the adenovirus infection. It was remarkable that three members of this family had a brief febrile episode with concurrent conjunctivitis during the month before the aforementioned infection. One of the children (Case 21) had complement-fixing antibodies *before* the onset of clinical symptoms of her type 3 infection.

fold and sometimes oedema of the eyelids. A viscous, adhesive exsudate occurred, especially in the mornings, in about half the cases. In detachment of the membranous covering, which was easily loosened, small punctate haemorrhages occurred. Keratitis and scleritis were not observed. In the milder cases there was only congestion of the palpebral conjunctiva.

A mild general *lymphadenopathy* was present in the majority of cases. Regional lymphadenitis was also observed, most pronounced along the

FIG. 4. Hospital outbreak of adenovirus type 3 infections.


NO. NAME SEX AGE DIAGNOSIS ROOM SYMPTOMS
SEPT. 20, 1955
OCT. 1
OCT. 15
NOV. 1
NOV. 15
DEC. 1
DEC. 15, 1955
JAN. 1, 1956
Suspected Diphtheria
JAN. 27
JAN. 1
22 I.L. ♀ 14 SC X
23 A.M ♂ 6 X
24 U.G ♀ 9 SC X
25 K.L ♂ 6 HS X
26 P.R ♂ 11 SC Diabetes X
27 A.L ♀ 7 SC X
28 A.H. ♀ 12 SC. X
29 I.B. ♀ 10 SC X
30 I.T. ♀ 7 SC X
31 B.K. ♀ 8 Nephritis X
32 I.S. ♀ 8 Nephritis X
33 E.S. ♀ 10 SC X
34 P.L. ♂ 9 SC X
35 M.K. ♀ 7 SC. X
36 E.L. ♂ 4 HS X
37 A.E. ♀ 10 SC X
38 K.G. ♂ 10 SC X
39 R.F. ♂ 6 SC X
40 T.T ♂ 9 SC X
41 T.L ♂ 9 SC. X
42 A.H. ♀ 9 SC X
43 B.L ♂ 8 SC X
44 C.N. ♀ 8 SC X
45 M.G. ♀ 9 Nephritis X
46 A.N. ♀ 9 SC X
47 K.N. ♀ 7 SC X
48 P.L. ♂ 8 SC X
49 U.L ♀ 7 SC X
50 G.H ♀ 6 SC X
51 B.N. ♀ 9 SC X
52 E.N. ♀ 6 SC X
53 M.L ♀ 11 SC X
54 G.K ♀ 9 SC X
55 M.W ♀ 5 HS X
56 K.J. ♂ 9 Rubella X
57 I.J. ♀ 7 SC X
58 A.J. ♀ 10 SC X
59 A.B. ♀ 6 SC X
60 M.W. ♀ 9 HS X
62 B.F. ♀ 28 STAFF
63 G.N. ♀ 23 STAFF


60 M.W. ♀ 9 HS X
62 B.T. ♀ 28 STAFF
63 G.N. ♀ 23 STAFF
65 K.G. ♀ 21 STAFF
66 S.N. ♂ 6 SC VIII C
67 I.N. ♀ 26 C
68 Å.K. ♂ 12 SC, V CAD L.P.
69 B.B. ♀ 6 SC, V A
70 B.B. ♂ 6 HS V A
JAN 26 MAY 14
MARCH 9

ABBREVIATIONS AND SYMBOLS

ADENOVIRUS TYPE 3 ISOLATION:
CONJUNCTIVAL +
PHARYNGEAL –
FAECAL SAMPLE +

++ NEUTRALIZING ANTIBODIES AGAINST TYPE 3
≥1:32 COMPLEMENT-FIXING ANTIBODIES

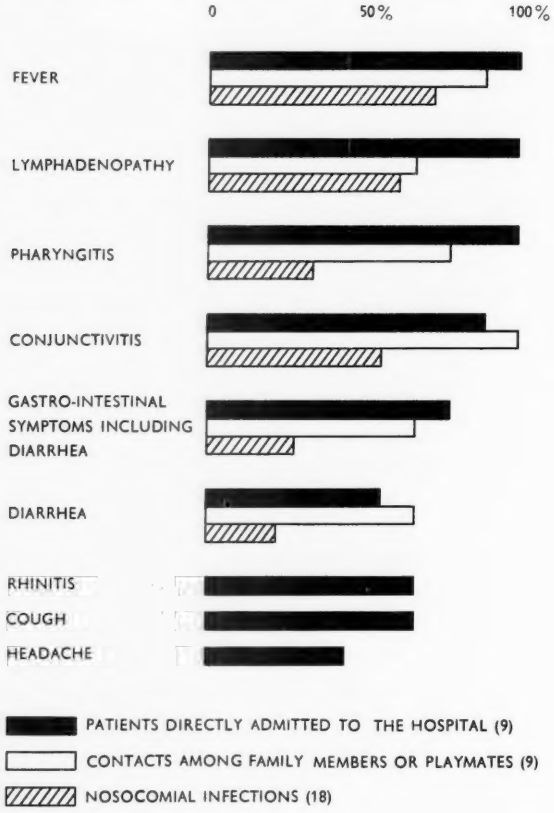
7 - ISOLATION OF ADENOVIRUS TYPE 7 OR NEUTRALIZING ANTIBODIES AGAINST TYPE 7

C - CONJUNCTIVITIS
A - ADENOPATHY
D - DIARRHEA
L.P - LUMBAR PUNCTURE

SC - SCARLET FEVER
SC, - SCARLET FEVER DESQUAMATION
HS - CARRIER OF β-HEMOLYTIC STREPTOCOCCIES
R - RUBELLA

40°C
BROKEN LINE = PERIOD OF OBSERVATION
SOLID LINE = PERIOD OF HOSPITALIZATION

FIG. 5. Clinical symptoms of 36 adenovirus type 3 infections in percentage.



sternocleidomastoid muscle and at the angles of the jaws. This regional lymphadenitis appeared proportional to the intensity of the *pharyngeal changes*. These consisted in turn of mild, non-characteristic pharyngitis without coating or enanthema. These pharyngeal changes could always be demonstrated objectively, but they gave subjective symptoms in only about half of the cases. Some signs of acute upper respiratory tract infection occurred in all cases, appearing as thin, nonpurulent nasal discharge, slight unproductive cough or mild pharyngeal symptoms. Two patients had *epistaxis*.

The *diarrhea* was relatively mild with two to three days' duration, without blood or mucus, and appeared concurrently with, or one to two days after, the onset of the fever. If we include nausea, vomiting and diarrhea among

the symptoms from the digestive tract, it may be seen from Fig. 5 that seven of nine patients had such symptoms. In no case did the gastrointestinal symptoms simulate an acute abdomen.

Symptoms suggesting an affection of the *central nervous system* occurred in the form of headache of varying intensity, pains in the legs and in the back of the neck and even stiff neck in a few cases. Whether or not the stiff neck was caused by tender lymph nodes in the neck could not be determined with certainty. Neurologic examinations, including lumbar puncture in four cases, were negative throughout. With regard to the facial paralysis (Case 18), see explanatory text accompanying Fig. 3.

The *complications*—all untreated—comprised two cases of sinusitis, verified by X-ray, and two cases of otitis simplex. No bacterial investigations were carried out on these. No cardiac changes, either clinical or electrocardiographic, were observed.

Laboratory tests.—The blood picture, both red and white cells, showed no significant change. The leukocyte count varied between 3900 and 11,300 without any characteristic shift in the differential count. No eosinophilia was demonstrated. The sedimentation rate varied between 4 and 42 mm with a mean of 27 mm.

The convalescence was without complication in all cases.

To sum up it may be said regarding these cases admitted directly to the Hospital, that, with their high fever, frequently strongly affected general condition, severe conjunctivitis, diarrhea and symptoms of the type of stiff neck and headache, they caused appreciable uneasiness among the population of the communities where they occurred epidemically. The disease was sufficiently characteristic to give rise to the local name "Kumla disease" after the name of the community where, according to the estimates of the local doctors, there were at least one thousand cases within a limited period. It should be emphasized that the patients described here were a selected group of the most severely affected in a large epidemic, and that the intensity of their symptoms contrasted sharply with those of the patients in the nosocomial outbreak described below.

II. Secondary Cases among Contacts

Eleven contact infections among family members and playmates of the foregoing patients were observed in Örebro under outpatient care. They were all traced on the basis of their clinical symptoms. In 7 of these patients (No. 7, 9–11 and 19–21) adenovirus type 3 was isolated. In an additional 2 cases (No. 15 and 16) the diagnosis was verified by rising or high antibody titers. Two family contacts (No. 12 and 14) were included due to their clini-

cal symptoms only; they are in this paper used only for the estimation of the incubation time.

With regard to the intensity of their symptoms, these 11 patients assumed, as might be expected, a middle position between the severe cases admitted directly to the Hospital on the one hand and the nosocomial infections on the other (Fig. 5). These contact cases proved especially useful in the determination of the incubation time (see text below).

III. Nosocomial Outbreak

Concurrently with the epidemic of adenovirus type 3 infections scarlet fever occurred endemically within the area served by the Hospital. According to the rule of the Hospital the majority of these patients pass through the isolation ward and not until the diagnosis is established are they placed in the larger rooms of the open ward, where they receive continued treatment with prolonged-effect penicillin (penditan) in weekly injections. When there is a shortage of beds, these patients may, however, be placed directly on an open ward.

On October 17, 1955, the day after her discharge from such an open scarlet fever ward, a seven-year-old girl developed symptoms of a clinically typical and virologically verified adenovirus type 3 infection (No. 9). Secondary cases thereafter appeared in the ward, where the child had been hospitalized. Fig. 4 shows the course of this nosocomial outbreak.

The entire patient material, with one exception (No. 67), comprised children aged between 4 and 12 years, with penicillin-treated, mild β-hemolytic streptococcus infections (cases of scarlet fever, desquamation after scarlet fever or mild nephritis, carriers of β-hemolytic streptococci), as well as one case of rubella (No. 56), admitted in error.

In one room (Room X with 10 beds) all the patients (Cases 22–61, Fig. 4) were followed with virus-diagnostic tests; in two other rooms (Room V with 7 beds and Room VIII with 3 beds) only clinically suspicious cases (No. 66–70) were included in this study. The patients were recorded in chronologic order. The solid lines of Fig. 4 represent the periods of hospitalization and the broken lines the observation periods before and after the hospitalization. The method of presentation thus makes possible a day-by-day survey of the situation, especially in Room X.

As shown by Fig. 4 the nosocomial outbreak continued over a period of about two months and during this time 18 adenovirus type 3 infections were diagnosed within the ward.

A retrospective study of the material suggests that patient No. 23 (cf. "cases directly admitted") and possibly No. 25 were the original sources of infection. The patients

No. 22, 24 and 27 presented no typical clinical symptoms and stool specimens for virus isolation were not produced during the period of observation; however, the presence of complement-fixing, and not only neutralizing, antibodies in late specimens suggests that these patients had recently gone through infections with adenovirus and may have been intermediary silent infections between No. 23 and the later nosocomial infections.

In 12 of the 18 nosocomial cases (No. 30, 31, 34, 43, 44, 47, 48, 50, 52 and 67–69) the diagnosis of an acute infection was established by isolation of adenovirus type 3, mainly from faeces, together with a significant rise in complement-fixing antibodies or a convalescent CF titer of at least 16. As a control, paired sera were also tested for neutralizing antibodies against type 3 in three of these patients (No. 43, 44 and 47), two of whom showed a definite increase.

In four other probably nosocomial infections (No. 38, 39, 46 and 53) the symptoms did not occur until a few days after the patients left the hospital. In these patients the virus isolation was negative before the development of clinical symptoms and not attempted thereafter, but the diagnosis was established on the basis of a significant rise in titer of both complement-fixing and neutralizing antibodies. With respect to the latter, the titration in acute phase serum was negative.

Patient No. 66, also included among the 18 nosocomial cases, was hospitalized in a nearby room (Room VIII) which shared toilet and lavatory with Room X. No faecal sample was obtained but the patient fell ill the day after discharge with a typical clinical picture and later specimens showed high titers of both complement-fixing and type-specific neutralizing antibodies. Ten days after the patient's return home the patient's mother (Case 67) presented a virologically verified and clinically typical type 3 infection. Patient No. 70 was included for similar reasons, although no secondary case was observed.

Patients No. 68–70 were hospitalized in a room at the other end of the ward (Room V) without known contact with Room X other than via the ward personnel. Attempts to demonstrate the presence of adenovirus in the ward personnel (No. 62–65) gave negative results with respect to adenovirus type 3, but instead type 7 was isolated from a ward aid (No. 63). The same type of virus was also recovered from the faeces of two patients in Room X (No. 46 and 51). These latter two patients exhibited no clinical signs of disease in conjunction with the demonstration of adenovirus type 7. The ward aid (No. 63) had a slight pharyngitis, without fever or other symptoms, for 4 days before the collection of specimens, but as titration of neutralizing antibodies against type 7 in paired sera showed unchanged high values the acute infection might in fact have occurred earlier.

Case 46 was especially interesting. The first time specimens were collected, adenovirus type 7, but not type 3, was isolated from the stools. In a blood specimen taken at the same time neither neutralizing antibodies against type 3 nor complement-fixing antibodies could be demonstrated. In a later blood specimen both complement-fixing antibodies and neutralizing antibodies against type 3 were shown. On the other hand, in both sera unchanged high titers of neutralizing antibodies against type 7 were

obtained. No clinical symptoms were noted either before or after the specimens were collected. The patient's sister (No. 47) had a definitely verified infection with adenovirus type 3 during her hospitalization. This case (No. 46) may be interpreted as being an asymptomatic double infection with a prolonged virus excretion after a previous type 7 infection, superimposed by an actual type 3 infection.

With regard to virus isolation it should, furthermore, be pointed out that, although the virus in most cases seemed to have disappeared from the faeces within two weeks, in one case (No. 69) repeated isolations were successful as late as three months after the onset of the disease. It may be mentioned here that one of the contacts (No. 21) excreted virus about one month after a typical illness. On the other hand, it is also remarkable that in two cases (No. 43 and 47) the virus was demonstrated in the faeces 2 and 5 days respectively before clinical signs of infection appeared.

The finding of complement-fixing antibodies in serum concurrently with negative stool tests and long before the onset of a definite type 3 infection (No. 38 and 39) may suggest a recent infection with another adenovirus type since otherwise the complement-fixing antibodies seem to appear after the onset of the clinical symptoms.

The clinical symptoms in these nosocomial cases were largely the same as in the foregoing groups, i. e. fever, conjunctivitis, pharyngitis and occasionally diarrhea (cf. Fig. 5). Throughout, however, these nosocomial infections were notably milder and without effect on the general condition or, in certain cases, purely asymptomatic or monosymptomatic (No. 31, 39, 44, 46, 52 and 53). As a matter of fact a number of cases were so mild that, if we had not been specially aware that a nosocomial infection was in progress and therefore examined the patients and temperature curves with particular care, several cases would never have been discovered. Practically all cases of conjunctivitis reported in Fig. 5 could be observed only on close inspection and the lymphadenopathy only on palpation. Diarrhea was also considerably more rare and less severe in this material than among the patients admitted directly to the hospital (10 per cent as opposed to 60 per cent). The fever, to the extent it occurred at all (50 per cent afebrile), was considerably lower, with a mean maximum temperature of 38°C as opposed to 39,8°, and of shorter duration, i. e. five as opposed to seven days. None of these nosocomial cases simulated affection of the central nervous system. Neurologic investigations including four lumbar punctures were negative throughout.

Inasmuch as the entire group, as mentioned earlier, with but one exception (No. 56) consisted of penicillin-treated infections with β-hemolytic streptococci, a discussion and analysis of the laboratory values showing the red and white blood cell picture, the differential count, sedimentation

rate, urine analysis, etc. seems meaningless. The possible effect of the β-hemolytic streptococci and the penicillin therapy on the course of the adenovirus infection will not be discussed here. It may be said, however, that there seems to have been no effect whatsoever on the spread of the infection.

Except for a slight bronchopneumonia, verified by X-ray and with negative cold agglutination, no *complications* occurred. Three electrocardiograms and two further pulmonary X-rays were negative.

Various Observations within the Three Groups of Infections with Adenovirus Type 3

The difficulties of determining an exact *incubation period* appeared almost insurmountable when the isolation of virus even before clinical signs of infection appear (No. 43 and 47) and the possibilities for contact with asymptomatic or monosymptomatic virus excretors (No. 31, 44, 52 and 69) were considered. The ideal opportunity for estimation of the incubation time was afforded by the cases in which the patients had contact on a single occasion (No. 13 and 15) where an incubation period of 10–11 days may be computed. It might be possible to obtain the minimum incubation time from the interval between primary and secondary cases where the patients were separated (No. 6 and 23, where the onset in members of the family was 6 and 11 days respectively after the separation). The interval between the discharge of a case and the first secondary case thereafter should also give rather definite incubation times (No. 15 and 16, 7 days' interval; No. 66 and 67, 10 days' interval), as should the interval between the first case and secondary case within one family (No. 10 and 7–9, 8 days; No. 3 and 14, 9 days; No. 19 and 18, 10 days). From the foregoing few cases we obtained an *incubation time* averaging 9 days. For the aforementioned reasons it seemed impossible to use the nosocomial outbreak described here for computation of incubation times.

Judging from the incidence of adenovirus in 4 family groups (Figs. 2 and 3) the contagiosity appeared high. The part of the nosocomial outbreak referable to Room X (No. 22–61, Fig. 4) afforded further possibilities for study of these conditions. All of the patients *passing through Room X*, with the exception of 4, who could not be recalled (No. 28, 29, 33 and 35) were examined for the presence of adenovirus in the faeces, in certain cases in the conjunctiva, pharynx and nose, and for complement-fixing and in most cases neutralizing antibodies. Among the 36 investigated patients and 4 personnel, exposed in Room X (No. 22–61 and 62–65, respectively) 14 infections with adenovirus type 3 were demonstrated (No. 23, 30, 31, 34,

38, 39, 43, 44, 46, 47, 48, 50, 52 and 53). In 21 of the remaining 26 exposed persons (22 patients and 4 personnel) neutralizing antibodies were demonstrated. Actually, no late serum specimens were available from two of the negative cases (No. 49 and 55). The presence of neutralizing antibodies may be interpreted as a sign of a previous infection, whether recent or not. Accordingly, there remained only 5 patients in this material (No. 36, 49, 55, 60 and 61) in whom, despite exposure, type-specific neutralizing antibodies could not be demonstrated, thus indicating high contagiosity of adenovirus type 3.

Patients No. 55, 60 and 61 had contact with definite adenovirus infections (No. 48 and 50) to be sure, but the virus excretion might possibly have ceased in these two cases before the contact occurred. If patients No. 55, 60 and 61 are preliminarily regarded as not exposed, only two patients, who failed to be infected, remain in the material.

For purposes of comparison it may be pointed out that Case 56 (rubella) gave rise to 6 secondary cases among a possible 7 (No. 48, 50, 55, 58, 60 and 61).

The material, which included mainly children from 5 to 12 years of age, with intensive contact in the hospital ward and in addition using the same lavatory and toilet room, did not permit any definite conclusions concerning the *pathways of communication of the disease.*

Comments

In the patient material presented here there was a good correlation in the cases admitted directly to the Hospital between the clinical symptom picture and the demonstration of a current infection with adenovirus type 3 by means of virus isolation and serological tests.

The discrepancy between the clinical symptoms in the directly admitted cases, on the one hand, and that in the nosocomial cases, on the other, was striking. The natural explanation would seem to have been that the directly admitted patients comprised a selected group of the most severe cases in a large epidemic, whereas the nosocomial cases to a greater degree than in earlier investigations included *all* type 3 adenovirus infections in an exposed group of patients (cf. Fig. 4). In the latter instance it appears as if the incidence of mild to monosymptomatic and, in certain cases, asymptomatic cases were considerably greater than that found by Bell *et al.* (3) for example. Their conclusion that there is 100 per cent correlation between symptoms and the presence of virus obviously does not correspond to our observations. There are several conceivable explanations for this.

One would seem to be that Bell's patient material was selected largely

on the basis of clinical symptoms, whereafter virus and antibody observations were correlated to them, while in our material virus and antibodies were demonstrated and the results thereafter correlated to any symptoms present.

On the other hand, our material was relatively small and not entirely pure seeing that it comprised convalescents, who had recently gone through a hemolytic streptococcus infection and who were on penicillin therapy during the entire observation period.

A difference in the pathogenicity of the various strains of adenovirus type 3 may also be discussed as a possible explanation to the discrepancies noted between American and Swedish observations. As pointed out elsewhere (3) it seems possible that the Swedish virus was more enterotropic than the strains encountered by Bell and coworkers. Thus the incidence of gastrointestinal symptoms was apparently much higher in the Swedish outbreaks (3). During the present investigation virus was found in the stools of acute cases more regularly than in specimens from the conjunctiva, nose and pharynx in concurrent isolation attempts. Actually, large amounts of virus were excreted in the stoools (3) and the excretion sometimes continued for months after the acute disease; even asymptomatic contacts excreted virus this way. Virus was also found in the sewage from epidemic areas (3). Obviously the adenovirus type 3 encountered in Sweden had appreciable similarities with the so-called enteric viruses, i. e. polioviruses, Coxsackie and ECHO viruses (3).

Considering that adenovirus in analogy with the last-mentioned viruses might have neurotropic properties and give rise to aseptic meningitis, possibly even asymptomatic ones, lumbar puncture was done in 8 cases in this material, all with negative results, however.

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Summary

The clinical and virologic aspects of 38 infections with adenovirus type 3 are described. The material includes 9 patients, admitted directly to the hospital and 11 cases resulting from contact with them, as well as 18 nosocomial infections. A striking difference seems to exist between these groups with respect to the incidence and intensity of the clinical symptoms. The nosocomial outbreak was largely limited to one room, where the patients were systematically examined for virus and antibody occurrence with *subsequent* correlation to clinical symptoms. It seems possible to draw the following conclusions from the investigation, in contrast, to a certain extent, to those reached by other investigators:

(1) It appears that adenovirus type 3 may be excreted with faeces several days before, during, as well as months after clinical signs of infection are manifested.

(2) It appears that the course of infections with adenovirus type 3 may often be asymptomatic or monosymptomatic and not always show the typical picture of pharyngoconjunctival fever.

(3) The virus was easily demonstrated in stool specimens and symptoms from the gastrointestinal tract primarily in the form of diarrhea occurred in a high percentage of the cases.

Consequently, when taken together with other reasons advanced by Kjellén, Zetterberg & Svedmyr (3), it seems justifiable to conclude that strains of adenovirus type 3 may have enterotropic characteristics similar to Coxsackie, ECHO and polioviruses to a greater degree than has been believed heretofore.

Epidémie par adénovirus, type 3, dans un hôpital. Etude clinique et virologique de 38 malades partiellement atteints par une épidémie nosocomiale.

Les aspects cliniques et virologiques de 38 infections par adénovirus, type 3, sont décrits. Le matériel comprend 9 malades hospitalisés directement, 11 individus qui furent en contact avec eux, et 18 cas d'infection nosocomiale. Une différence frappante semble exister entre ces groupes en ce qui concerne l'incidence et l'intensité des symptômes cliniques. L'épidémie nosocomiale fut en grand partie limitée à une seule salle, où les malades furent systématiquement examinés, avec étude du virus et de la présence d'anticorps et corrélation subséquente avec les symptômes cliniques. On croit pouvoir tirer de cette investigation les conclusions suivantes, qui, jusqu'à un certain point, sont en contradiction avec celles atteintes par d'autres chercheurs. 1) Il semble que l'adénovirus, type 3, puisse être excrété avec les fèces plusieurs jours avant et pendant la manifestation des signes cliniques de l'infection, ainsi que pendant des mois après. 2) Il semble que le cours de l'infection par adénovirus, type 3, soit souvent asymptomatique ou monosymptomatique et que le tableau clinique ne soit pas toujours caractéristique de la fièvre pharyngo-conjonctivale. 3) Le virus fut facilement isolé des selles et des symptômes gastro-intestinaux, surtout sous forme de diarrhée, furent présents dans un pourcentage élevé de cas. Par conséquent, en tenant également compte d'autres raisons avancées par Kjellén, Zetterberg et Svedmyr, il semble justifiable de conclure que les souches d'adénovirus, type 3, aient des caractéristiques entérotropes semblables aux virus Coxsackie, ECHO et de la poliomyélite, à un degré plus important qu'on ne le croyait jusqu'à présent.

Ausbruch einer Typus 3 Adenovirusinfektion im Krankhenhaus. Klinisches and virologisches Studium von 38 zum Teil in einer nosokomialen Infektion mitbeteiligten Kranken.

Die klinischen und virologischen Gesichtspunkte bei 38 Fällen von Typus 3 Adenovirusinfektion werden beschrieben. Das Material schliesst 9 Kranke ein, die direkt ins Spital aufgenommen wurden und 11 aus dem Kontakt mit ihnen sich ergebende Fälle, sowie 18 nosokomiale Fälle. Es scheint ein auffallender Unterschied zwischen diesen Gruppen mit Rücksicht auf das Wesen und die Intensität der klinischen Symptome zu bestehen. Der nosokomiale Ausbruch war wesentlich auf ein Krankenzimmer beschränkt, wo die Kranken mit Bezug auf das Vorkommen von Viren und Antikörpern systematisch untersucht und die Ergebnisse mit den klinischen Symptomen nachher in Beziehung gebracht wurden. Aus der Untersuchung lassen sich, wie es scheint, folgende, bis zu einem gewissen Grad von den von anderen Arbeitern erreichten ab-

weichende Schlüsse ableiten: 1) Es scheint, dass Adenovirus Typus 3 mehrere Tage vor dem Auftreten klinischer Zeichen, während seines Bestehens und noch monatelang nach seinem Abklingen in Stuhle ausgeschieden wird. 2) Der Ablauf einer Typus 3 Adenovirusinfektion kann anscheinend symptomlos oder nur von einem Symptom begleitet sein und nicht immer das typische Bild eines pharyngo-konjunktivalen Fiebers aufweisen. 3) Das Virus war in Stuhlpräparaten leicht nachzuweisen und gastrointestinale Symptome, vorwiegend in der Form von Durchfällen, kamen bei einem grossen Prozentsatz der Fälle vor. Wenn andere Umstände, die von Kjellén, Zetterberg und Svedmyr angeführt wurden, mitberücksichtigt werden, dann erscheint der Schluss gerechtfertigt, dass Typus 3 Adenovirusstämme ähnlich wie Coxsackie, ECHO und Polioviren enterotropische Charakterzüge in grösserem Grad besitzen, als bisher angenommen wurde.

Brote de infecciones adenovíricas Tipo 3 en un hospital. Estudio clínico y virológico de 38 enfermos parcialmente afectados por un brote nosocomial.

Descripción de los aspectos clínicos y virológicos de 38 casos de infecciones adenovíricas del tipo 3, incluyendo 9 pacientes ingresados directamente en el hospital y 11 casos que resultaron infectados a consecuencia de contacto con aquellos, así como 18 infecciones nosocomiales. Parece existir una diferencia sorprendente entre estos grupos, con respecto a la incidencia e intensidad de los síntomas clínicos. El brote nosocomial se limitó mayormente a una sala, donde los pacientes fueron examinados sistemáticamente con respecto a la aparición de virus y anticuerpos subsiguientemente correlacionados con los síntomas clínicos. Parece posible sacar las siguientes conclusiones de la investigación, en contraste, hasta cierto punto, con las que sacaran otros investigadores: 1) Aparece que el adenovirus tipo 3 puede ser exretado con las heces varios días antes, durante, así como meses después de manifestarse los síntomas clínicos de infección. 2) Aparece que le curso de las infecciones de adenovirus tipo 3 pueden ser frecuentemente asíntoma o monosintomáticas y que no siempre presentan el cuadro típico de fiebre faringoconjuntiva. 3) La presencia del virus ha sido comprobada fácilmente en muestras de deposiciones, induciéndose, en un alto porcentaje de los casos, síntomas de origen gastronintestinal, primariamente manifiestos en forma de diarrea. Por consiguiente, considerado el conjunto con otras razones adelantadas por Kjellén, Zetterberg y Svedmyr, parece justificada la conclusión de que las cepas de adenovirus tipo 3 presentan similitud, en mayor grado de lo que hasta ahora se creíca, con las características enterotrópicas de los virus de Coxsackie, ECHO y poliomielitis.

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The Blood Sugar in Cyclic Vomiting

by L. SALOMONSEN and KR. HARNÆS

Serious cases of cyclic vomiting with marked ketosis and dehydration, deep Kussmaul air-hunger respiration, drowsiness or coma, can easily suggest a diabetic coma. There is a widespread belief that the determination of the blood sugar is a valuable aid in the differential diagnosis. Since the publications of Hilliger (1914) and Ross & Josephs (1924), *hypoglycaemia* was considered a characteristic finding in cyclic vomiting. This is repeated in most paediatric textbooks, Fanconi–Wallgren (1956, v. Creveld), Nelson (1954, Waldo Nelson), *Nordisk Lærebog i Pædiatri* (1956, Siwe), Brennemann (1948, Parmelee), Bamberg, Degkwitz *et al.* (1942, Rominger), and Feer (1938, Kleinschmidt).

Only in the British literature do we find differing statements. Thus in Paterson & Moncrief's textbook (1947), it is stated that the blood sugar can be elevated, and that there may be glycosuria. In a discussion on cyclic vomiting (*Proceedings of the Royal Soc. of Medicine*, 1951), Hamilton & Payne hold the same view.

The reason why hypoglycaemia is considered to be present in attacks of cyclic vomiting, is in all probability due largely to the confusion of cases of true cyclic vomiting with the metabolic reaction with ketonaemia and vomiting that can be provoked in children by suddenly placing them on a diet poor in carbohydrates. In this reaction, which is not true cyclic vomiting, hypoglycaemia is a constant finding.

In the true case of idiopathic cyclic vomiting, hypoglycaemia is far from constant. The blood sugar values in the first phase are extremely variable. They can be reduced or they can be normal, and not rarely one finds *hyperglycaemia*. The statement that hypoglycaemia is a constant finding is diagnostically misleading, and should be abandoned.

High blood sugar values in the first phase of the attack, before the institution of treatment, have been found amongst others by Curschmann (1930): 156, 170 and 150 mg% in three different attacks in the same patient; Åkerrén (1931): 152 mg%; Salomonsen & Bjelke (1932): 183 mg%. Two of Ström's cases (1935) had blood sugar values of 133 mg% and 154 mg% respectively.

To these reports the following two cases can be added:

TABLE 1

Laboratory findings. Patient 1.

	$^{21}/_{11}$		$^{22}/_{11}$		$^{23}/_{11}$	$^{24}/_{11}$
Blood						
Blood sugar, mg %	327	400[a]	203	129[a]	91	114
CO_2, vol. %	10.0	21.8[a]	31.4		44	65.9
Chlorides, m.eq./l	107		107		109	105
Urea, mg %	72		38			
Urine						
Sugar (Benedict)	÷		÷		÷	
Ketone bodies	+ + +		+ + +		+	

[a] Eight hours' interval between the two determinations.

CASE 1.—I. M., A 2½ year old psycholabile girl. No previous attacks of cyclic vomiting. From Nov. 20, 1955, persistent vomiting. Admitted Nov. 21, 1955, in a state of shock, dehydrated, drowsy, deep respiration. Normal temperature. The rest of the examination negative. Laboratory findings: see Table 1. Treated with intravenous fluid administration (blood, sodium lactate, saline, glucose, Darrow's solution); marked improvement, cessation of vomiting. Completely recovered on the fourth day.

CASE 2.—O. B., 3 year old boy. No previous attacks of cyclic vomiting. From April 25, 1957, intense persistent vomiting. Admitted April 26, 1957, in a state of shock, marked dehydration, deep breathing, restless, drowsy. Normal temperature. The rest of the examination negative. Laboratory findings: see Table 2. After intravenous administration of saline, sodium lactate, glucose, Darrow's solution, marked improvement. Completely recovered on the fourth day.

Laboratory findings. Patient 2.

TABLE 2

	$^{26}/_{4}$		$^{27}/_{4}$	$^{28}/_{4}$	$^{29}/_{4}$	$^{30}/_{4}$
Blood						
Blood sugar, mg %	276	140[a]	100	95	87	
CO_2, vol. %	10.0	24.2[a]	31.9			
Chlorides, m.eq./l	115	105[a]	104			
Urea, mg %	116.2					
Urine						
Sugar (Benedict)	+		÷	÷	÷	
Ketone bodies	+ + +		+ +	+ +	+ +	+

[a] Eight hours' interval between the two determinations.

Thus in two children with a typical attack of cyclic vomiting, we find blood sugar values of 327–400 mg% and 276 mg% respectively. One case simultaneously had glycosuria. In neither of the two cases had there been previous administration of sugar or other carbohydrates.

The glucose tolerance curve, shortly after recovery, was normal in the first patient. In the second patient the curve was somewhat high and prolonged, as also other authors have found (Ström, 1935, and others). One month later this patient had a normal glucose tolerance curve.

The reason for the variable blood sugar values in attacks of cyclic vomiting is open to discussion. A possible cause of hyperglycaemia could be increased production of adrenal hormones, partly of adrenaline and partly of glycocorticoids, as a result of the stress situation created by the attack. Both would lead to increased blood sugar values.

Summary

It is pointed out that not rarely one finds increased blood sugar values in the first phase of an attack of cyclic vomiting. Reference is made to two patients who had blood sugar values of 327–400 mg% and 276 mg% respectively, on the second day of their illness.

The belief that an attack of cyclic vomiting is accompanied by hypoglycaemia should be revised. It can be misleading, especially in the differential diagnosis against a diabetic coma.

La glycémie dans le vomissement cyclique.

L'auteur attire l'attention sur le fait qu'il n'est pas rare que l'on observe de l'hyperglycémie au cours de la première phase d'une crise de vomissements cycliques. Il cite les cas de deux malades chez lesquels le taux de la glycémie s'élevait respectivement à 327–400 mg% et à 276 mg% le deuxième jour de la maladie. L'opinion suivant laquelle les vomissements cycliques s'accompagnent d'hypoglycémie doit être revue. Cette théorie peut conduire à des interprétations erronées, notamment lors du diagnostic différentiel vis-à-vis d'un coma diabétique.

Der Blutzucker bei zyklischem Erbrechen.

Es wird auf die Tatsache hingewiesen, dass vergrösserte Blutzuckerwerte gar nicht so selten während der ersten Phase von zyklischem Erbrechen angetroffen werden. Zwei Fälle werden angeführt, die Blutzuckerwerte von 327–400 mg% und beziehungsweise 276 mg% am zweiten Krankheitstage aufwiesen. Die Meinung, dass ein Anfall von zyklischem Erbrechen von Hypoglykämie begleitet sei, ist revisionsbedürftig. Sie kann, besonders bei der Differenzialdiagnose mit diabetischem Koma, irreführend sein.

La glucemia en los vómitos cíclicos.

Señálase que no es infrecuente encontrar valores aumentados de azúcar en la sangre, en la primera fase de un ataque de vómito cíclico. Refiérese a dos pacientes acusando

valores de azúcar en la sangre, de 327–400 mg% y 276 mg% respectivamente, e segundo día de la enfermedad. Precisaría revisarse el criterio de que el ataque d vómito cíclico está acompañado con hipoglicemia. Puede desorientar, especialmente en el diagnóstico diferencial del coma diabético.

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Scintillometric Length of Uterus during Adolescence

by ERIK ODEBLAD and CARL GUSTAF BERGSTRAND

For proper description of the developmental condition during adolescence in girls it is of great value to record the clinical effects of the ovarian estrogenic activity. Besides titration of urinary estrogens, which gives a momentary picture of ovarian function, the integrated activity of estrogenic hormones on the growth of e.g. mammary glands and uterus and the occurrence of menstruation is often recorded clinically. Of these signs the estimation of the size of uterus is the most subjective and inaccurate procedure. Since a simple technique has been developed for measuring directly a length related to the size of the uterus for clinical purposes (Odeblad, Englund & Meurman, 1957; Odeblad & Englund, 1958) we decided to apply this technique to a study of the uterus during adolescence. For further information about the technique and its sources of error the reader should consult these papers.

Material

Girls suffering from a disease of extra-ovarian nature (convulsions, duodenal ulcer, fever of unknown etiology, etc.) in the pediatric clinic, as well as girls subjected to routine health examinations were selected for this study. The ages were between 8 and 25 years. The girls were subjected to a complete physical examination including development of genitalia and mammary glands, pubic hair and other secondary sex characters and the recording of menstrual data. Height, span, upper and lower segment and weight were also registered. In some cases it was possible to take a vaginal smear for cytologic examination. The size, shape, position and flexion of the uterus were recorded by subjective estimation at pelvic examination as well as the approximate ratio of corporeal to cervical lengths. The occurrence of cervical secretion was noted either from history or from the bimanual examination. The examinations were undertaken irrespective of the day of the menstrual cycle since present evidence (Odeblad, 1958) indicates that the variation with the menstrual phase is small both in luteal and aluteal menstrual cycles. A total of 153 girls were examined.

Technique

The technique described by Odeblad, Englund & Meurman (1957) with the modifications reported by Odeblad & Englund (1958) was applied. The principle of this method (Fig. 1) is that a radioactive point source is attached to the inner finger at the bimanual

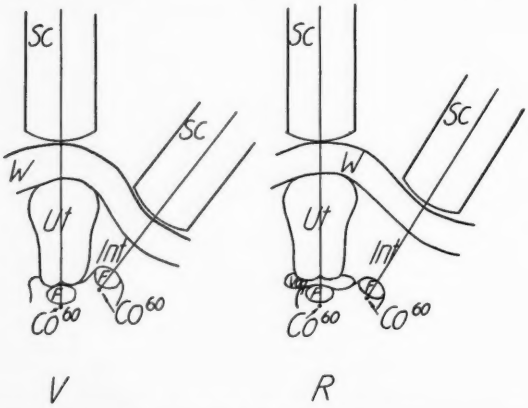

Fig. 1. Principle for a vaginal (V) and rectal (R) scintillometric investigation of uterine size. Co^{60} denotes radioactive source, F denotes finger introduced in vagina or rectum and carrying the source. *Sc* is the scintillation detector, the front of which is spherical around the radiologic centre of the crystal. *W* denotes abdominal wall, *Ut* denotes uterus, *Vag* denotes vagina and *Int* interposed tissues when measuring the lateral distances. The uterine length U is the difference between central and lateral distances and can be obtained either at vaginal (U_V) or rectal (U_R) examination. Reference is also made to illustrations in the papers by Odeblad, Englund & Meurman (1957) and Odeblad & Englund (1958).

examination, while a directional scintillation detector records the gamma counting rate at the position of the outer fingers. A ratemeter was used for recording the impulse rate, which varied between 9000 and 25,000 impulses per minute in different readings. The counting rate is a function of the distance between the inner finger and the outer hand. By measuring in this way the distance over the uterus or immediately beside the uterus is obtained. A difference in length, U, is thus obtained by simple subtraction, closely related to the size of the uterus.

Most of the younger girls were examined by rectal examination. In those cases where the vaginal opening permitted one finger to be introduced without difficulty, scintillometry per vaginam was undertaken in order to obtain scintillometric values comparable with the figures obtained for adult women (Odeblad & Englund, 1958). A comparison of the vaginal and rectal routes for scintillometric examination was also undertaken in the present work.

Radiation Dose

The source of Co^{60} had a strength of about 3 μC and was applied dorsally on the internal examining finger. Each measurement required a maximum time of about one minute, because the ratemeter time constant was put as low as 2.5 seconds, and the necessary equilibration time was consequently only about 15 seconds. The accumulated dose on the ovaries was estimated to about 0.1 mr, a dose far below the permissible level of 300 mr and corresponding to the continuous exposure from cosmic radiation and natural body radioelements (H^3, C^{14}, K^{40}, Rb^{86}) for about a week (see Tables 1 and 2). For comparison, it may be mentioned that a 12-hour flight at 8000 m gives an accumulated dose of about 1 mr from cosmic radiation (see Tobias, 1952).

TABLE 1

Radiation exposure from a 3 μC Co^{60} gamma ray source.

Artificial radiation		
Distance from source, cm	Dose rate mr/min	Typical organ exposed
0.3	7	Closest portion of vaginal and rectal mucosa, nail of investigator
1	0.7	Portio
2	0.1	Ovary, cervical mucosa
3	0.07	Uterine mucosa, intestine

TABLE 2[a]

Natural source	Dose rate mr/week	Basis for calculation	Reference
H^3 in body	0.01	$H^3/H^1 = 10^{-18}$	Kaufman & Libby, 1954
C^{14} in body	0.03	0.4 dis. min^{-1} (g tissue)$^{-1}$	Anderson & Hayes, 1956
K^{40} in body	0.4	28 dis. sec^{-1} (g K)$^{-1}$	Endt & Kluyver, 1954
Rb^{87} in body	0.4	$Rb^{87}/Rb = 0.28$, $T_{\frac{1}{2}} = 6 \times 10^{10}$ years Rb/K = 0.02	Hollander, Perlman & Seaborg, 1953
Cosmic radiation[b]	1	—	Lea, 1955
Total	1.5		

[a] This table does not account for the increasing global accumulation of Cs^{137} in tissues from nuclear explosions. Bone seekers, such as Ra^{226}, Sr^{90} and others are not tabulated here.

[b] Cosmic radiation at flight at 8000 m: 15 mr/week.

For calculation of these dose figures references are found in Table 2. The radiation dose here is smaller by a factor of about 100 as compared with the exposure of a diagnostic X-ray examination of the abdomen. The radiation dose at the examination must therefore be regarded as quite negligible.

Results and Discussion

Values of U obtained at rectal and vaginal examination are shown in Fig. 2 for various ages and show a tendency to increase with age. The rectal values were extended to much younger girls than the vaginal values and show nicely the rapid growth of the uterus between 12 and 14 years. The values of U at rectal and vaginal examination in relation to menarche

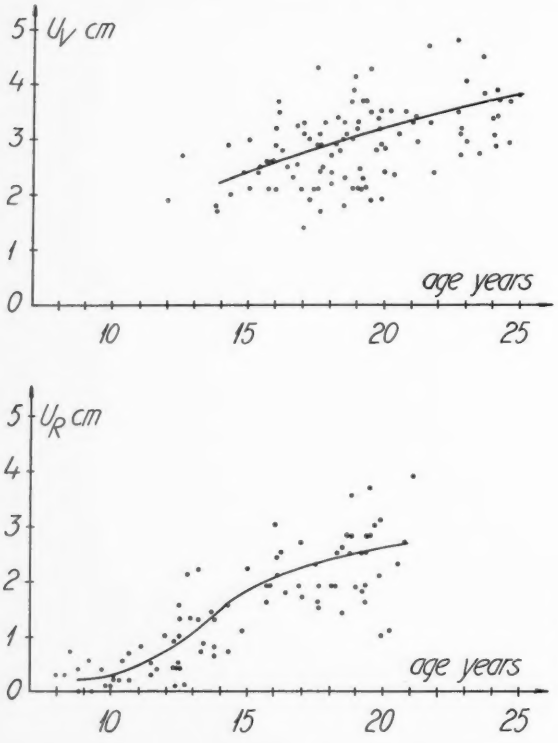

Fig. 2. Magnitude of U in cm by rectal (U_R) and vaginal (U_V) examination in relation to chronologic age.

are shown in Fig. 3. It is evident that when the menarche occurs, the uterus has, to a large extent, already grown considerably. The values of U grouped according to the estimated degree of development of other secondary sex characters are shown in Fig. 4. When looking at the results shown in this figure one has the general impression that the scintillometric size of uterus will be a good indicator of development in adolescent girls.

A comparison of our results with the uterine weight data of Wehefritz (1924) is of interest and is shown in Fig. 5.

The correlation between U obtained by the rectal and by the vaginal route is shown in Fig. 6. The smaller value of U obtained at rectal examination is due mainly to an increase of D_L when examining via the rectal route. This is in turn probably due to the higher muscular tonus of the rectal wall compared with that of the vaginal wall. We had, in addition, the impression that the vaginal route was a little more certain than the rectal route. For practical purposes the rectal route is well applicable.

The scintillometric procedure is not difficult to apply, but needs experience

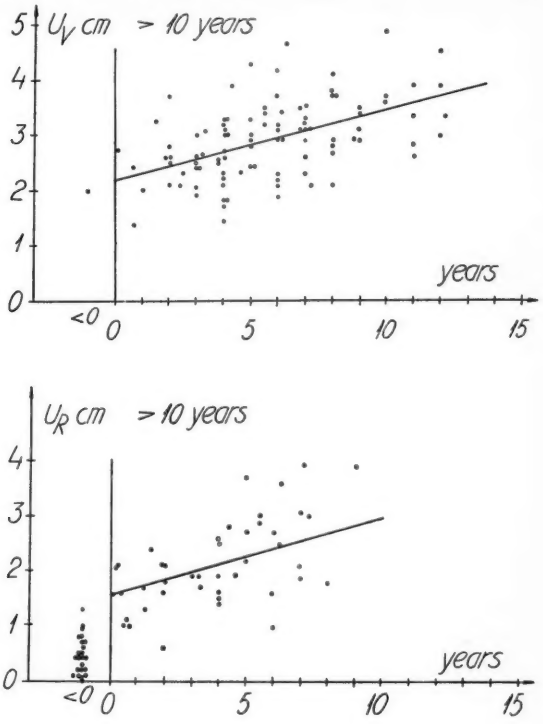

Fig. 3. Magnitude of U in cm by rectal (U_R) and vaginal (U_V) examination in relation to time after menarche.

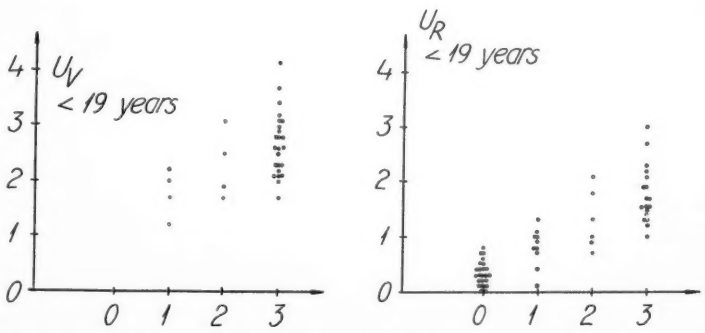

Fig. 4. Magnitude of U in cm by rectal (U_R) and vaginal (U_V) examination grouped according to other secondary sex characters: 0, abscence; 1, slight presence; 2, moderate presence; 3, well-developed secondary sex characters.

before being used in practise. It should be remembered that it is only a supplement to the general, endocrinological or gynecological examination in the young girl, but that it yields a figure reproduceable within the method

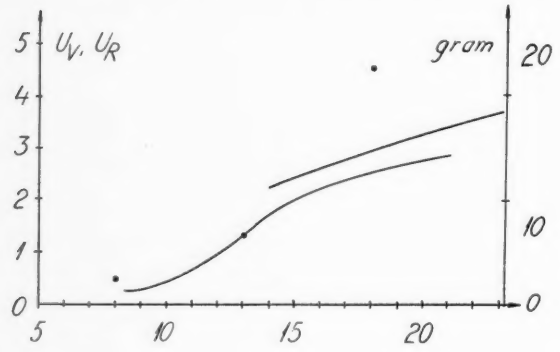

Fig. 5. Comparison of our U_R and U_V data with the uterine weight data of Wehefritz (1924). °, Uterine weight in grams.

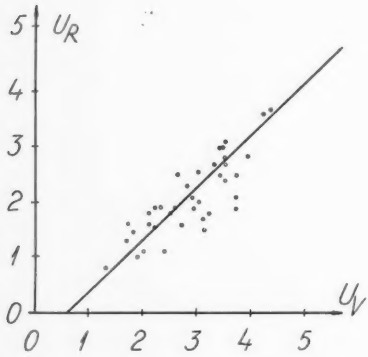

Fig. 6. Correlation between U by vaginal (U_V) and rectal (U_R) examination.

error, which by "double" determinations in 22 cases was evaluated to about ± 0.3 cm.

Both the vaginal and rectal values presented in this paper are available as a normal reference in diagnostic clinical applications.

Summary

The size of the uterus was determined with the method of scintillometry in adolescent girls. The correlation between age and uterine size showed large variations. The correlation between other signs of estrogenic activity and uterine size showed better correlation. A relation between time after menarche and uterine size is also presented. A comparison is made between the rectal and vaginal routes of scintillometry of the uterus. The diagrams are available as a normal reference in clinical applications.

La longueur scintillométrique de l'utérus pendant l'adolescence.

L'auteur a procédé à des déterminations des dimensions de l'utérus par la méthode scintillométrique chez des adolescentes. Il est apparu qu'il n'existe pour ainsi dire

aucune relation entre l'âge des intéressées et les dimensions de l'utérus. D'autre part, il semble qu'il existe une certaine corrélation entre les autres signes de l'activité œstrogène et les dimensions de l'utérus. De même, il semble qu'il y ait également une corrélation entre les dimensions de l'utérus et le temps qui s'est écoulé de depuis la puberté. L'auteur établit ensuite une comparaison entre la scintillométrie de l'utérus par voie vaginale et par voie rectale. Les diagrammes peuvent servir de référence pour les applications cliniques de cette méthode.

Scintillometrische Längenmessung am jugendlichen Uterus.

Die Grösse des Uterus wurde bei heranwachsenden Mädchen mit Hilfe der scintillometrischen Methode bestimmt. Die Wechselbeziehung zwischen Alter und Uterusgrösse wies grosse Schwankungen auf. Die Wechselbeziehung zwischen anderen Zeichen von östrogener Tätigkeit und Uterusgrösse war mehr einheitlich. Eine Beziehung zwischen der Zeitspanne seit der Menarche und der Uterusgrösse ist auch aufgezeigt. Die rektale Route für die Scintillometrie des Uterus wird mit der vaginalen verglichen. Die Diagramme werden für normale Bezugnahme zur Anwendung in der Klinik dargeboten.

Crecimiento centelleante del útero durante la adolescencia.

Determinación del tamaño del útero en mocitas adolescentes, por el método de la centelleometría. La correlación entre la edad y el tamaño del útero, presenta variaciones considerables. La correlación entre otros síntomas de actividad estrógena y el tamaño uterino, es mejor. Además, consideración de la relación entre la época postmenárquica y el tamaño uterino. Comparación de las rutas rectal y vaginal de la centelleometría uterina. Se dispone de los diagramas a título de referencia normal para aplicaciones clínicas.

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Aus dem Institut für Mikrobiologie und Immunologie, der Infektionsabteilung und der Rheumatologischen Abteilung der Universitätsklinik in Pilsen

Die Bedeutung der Streptokokkeninfektion für die immunologische Reaktivität des Makroorganismus[1]

von VLADIMÍR ZAVÁZAL, EVA BOŘÍKOVÁ, JOSEF WEIDENHOFER und JOSEF LAVIČKA

In der letzten Zeit wurde festgestellt, dass man nach der immunologischen Reaktivität noch in der gesunden Population diejenigen Personen ausfindig machen kann, welche zum Ausbruch des akuten Gelenkrheumatismus neigen (1, 2, 3). Es zeigte sich nämlich, dass grösstenteils die Personen, die hyperergisch reagierten, später nach einer Streptokokkeninfektion an akutem Gelenkrheumatismus erkrankten (2). Die Rolle der Hyperreaktivität in der Pathogenese dieser Krankheit scheint also sehr wichtig zu sein. Man muss aber damit rechnen, dass die immunologische Reaktivität nicht stabil sein wird, sondern sich im Zusammenhang mit vielen äusseren und inneren Einflüssen ändern wird. In dieser Mitteilung untersuchen wir, ob eine Streptokokkeninfektion die immunologische Reaktivität in Richtung zur Hyperreaktivität beeinflussen und den Weg zu einem weiteren pathologischen Prozess im Organismus freimachen kann. Wir beobachteten zwei Kindergruppen, die entweder eine unbehandelte oder mit Antibiotika behandelte Streptokokkeninfektion durchgemacht hatten und verglichen ihre Reaktivität mit den Kontrollgruppen.

Material und Methoden

Die Gruppe 1 bestand aus 10jährigen Kindern, die wegen Scharlach in der Infektionsabteilung 8 Tage mit Penicillin behandelt wurden. Bei allen 94 Kindern handelte es sich um typische Erkrankung mit Fieber, Scharlachangine und Scharlachexanthem. Bei keinem Kind traten in der Rekonvaleszenz Komplikationen auf.

Die Gruppe 2 bestand aus 87 Mitgliedern eines Lehrlingskollektivs in einem Brauhaus in Pilsen. Die Lehrlinge arbeiteten hier bereits ein Jahr in dauernd feuchtigem Arbeitsmilieu. In diesem Kollektiv verlief ohne ärzlichen Eingriff eine starke Streptokokkenepidemie, aus welcher 4 Fälle des akuten Rheumatismus resultierten. Etwa 10 Tage nach Ablauf der Epidemie wurde von uns die Untersuchung durchgeführt. Wir teilten

[1] Statistische Mitarbeit: Vladimír Malý. Technische Mitarbeit: Jiřina Čapková.

TABELLE 1

Die inkompletten Antikörper nach dem Brucella-Impuls bei der mit Penicillin behandelten Streptokokkeninfektion und bei der Gruppe gesunden Personen.

Gruppe	Titer der inkompletten Antikörper								
	0	20	40	80	160	320	640	1280	Zusammen
Gruppe 1	2	6	10	20	26	16	11	3	94
Kontrollgruppe		1	3	6	6	6	1	2	25

das Kollektiv in eine Gruppe A und eine Kontrollgruppe B ein. Gruppe A bestand aus Lehrlingen, welche eben die Streptokokkeninfektion durchgemacht hatten und zur Zeit der Untersuchung noch einen positiven Kultivationsbefund zeigten; in Gruppe B waren die übrigen Lehrlinge, die zwar keine offenbare Streptokokkeninfektion durchgemacht hatten, aber bei denen der Kontakt mit den Streptokokken nicht ausgeschlossen war. Die Reaktivität beider Gruppen wurde mit einer Kontrollgruppe von Knaben gleichen Alters, die bei guten hygienischen Bedingungen arbeiteten, verglichen.

Die Untersuchung der Reaktivität wurde bei allen Gruppen in derselben Jahreszeit durchgeführt. Der Antigenimpuls wurde mit Brucellabakterien der Dichte Nr. 2 nach McFarland-Skale durchgeführt und zwar in der Gruppe 1 bei der Entlassung der Kinder in die Hauspflege, in der Gruppe 2 zur Zeit des Vorkommens der ersten Rheumatismusfälle, also 7–14 Tage nach der Infektion. Es wurde 0,5 ml des Bakterins subkutan verabreicht. Vor der Impfung wurde ein Blutmuster zur Kontrolluntersuchung der kompletten und inkompletten Brucellaantikörper entnommen. Bei allen Untersuchten zeigte diese Kontrolle ein negatives Ergebnis. Die immunologische Reaktivität wurde 14 Tage nach der Immunisation durch Titration der inkompletten Antikörper bestimmt. Wo der Titer der inkompletten den der kompletten nicht überstieg, wurde vorausgesetzt, dass er mit dem Titer der kompletten identisch ist. Nähere Angaben über die Methodik sind in Arbeiten von Wagner u.a. angeführt (1, 3).

Ergebnisse

Die Ergebnisse führen wir in Tabellen an. In der ersten Tabelle wird die immunologische Reaktivität bei der Gruppe 1 und bei der entsprechenden Kontrollgruppe verglichen. Es zeigte sich, dass die Titer nach der behandelten Streptokokkeninfektion und bei der Kontrollgruppe fast nicht differieren. Die statistische Ermittlung zeigte, dass es zwischen diesen beiden Gruppen wirklich keine Differenz gibt. In Tab. 2 bringen wir die Reaktivitätsresultate beider Gruppen des Lehrlingskollektivs, in welchem eine unbehandelte Streptokokkeninfektion durchlief. Es zeigte sich, dass die Antikörpertiter in Gruppe A signifikant höher waren als in Gruppe B und der Kontrollgruppe. Es ist aber ersichtlich, dass auch in der Gruppe B die Reaktivität höher ist als in der Kontrollgruppe, obzwar gemäss der statistischen Ermittlung dieser Unterschied gerade an der Grenze der statistischen Bedeutsamkeit liegt.

TABELLE 2

Die inkompletten Antikörper nach dem Brucella-Impuls bei der unbehandelten Streptokokkeninfektion und bei den Kontrollgruppen.

Gruppe	Titer der inkompletten Antikörper									
	0	20	40	80	160	320	640	1280	2560	Zusammen
Gruppe 2 A				1	5	6	9	9		30
Gruppe 2 B	2	5	2	4	15	8	9	8	4	57
Kontrollgruppe		3	2	11	5	2	7	1		31

Diskussion

Den Anteil der Streptokokken an der Entstehung des akuten Gelenkrheumatismus kann man heute für nachgewiesen halten, wenn auch noch nicht klar ist, durch welchen Mechanismus die Streptokokken an der Entstehung des rheumatischen Prozesses teilnehmen. Wenn man eine enge Beziehung der immunologischen Hyperreaktivität zum Vorkommen des akuten Rheumatismus nachweisen konnte, bietet sich ein weiterer Weg zur Erklärung des pathogenetischen Mechanismus. Wir verfolgten vor allem die Bedeutung der Streptokokkeninfektion für die Dynamik der Reaktivität des Makroorganismus. Es war aber sehr schwer, passende Kollektive zu finden, da die Mehrzahl der Streptokokkeninfektionen heute richtig mit Penicillin behandelt wird, so dass der Streptokokkenimpuls von sehr kurzer Dauer ist. Für unsere Verfolgung bemühten wir uns, zwei Kollektive auszuwählen: eines, bei welchem die Streptokokkeninfektion durch moderne Therapie behandelt wurde und ein zweites, bei welchem die Infektion ohne ärzlichen Eingriff verlief. Im ersten Fall haben wir diese Forderung vollkommen erfüllen können; im zweiten Falle hatten wir zwar die Möglichkeit, ein Kollektiv, in dem eine Streptokokkenepidemie ohne Therapie durchlief, zu finden, aber die Zahl der Untersuchten konnte hier nicht gross sein. Wenn man heute keine passendere Methode zur Feststellung der immunologischen Reaktivität als das angeführte Brucellasystem zur Verfügung hat, kann man auch nicht verlässlich voraussetzen, dass die verfolgten Kollektive vor der Streptokokkenerkrankung die den Kontrollgruppen entsprechende Reaktivität gehabt haben. Diese Voraussetzung scheint uns aber höchst wahrscheinlich, denn sie wurde schon früher von anderen Autoren indirekt nachgewiesen (1, 2, 3).

Aus den Resultaten geht hervor, dass eine rechtzeitig und lange genug mit Penicillin behandelte Streptokokkeninfektion für den Makroorganismus keinen so intensiven Impuls bedeutet, der zur allgemeinen Reaktivitätsveränderung führen könnte. Diese Beobachtung ist in Übereinstimmung mi

der seltenen Erscheinung des akuten Rheumatismus nach Scharlach, bei welchem die Therapie und Isolierung gut verwirklichbar sind. In der Gruppe der unbehandelten Streptokokkeninfektion wurde aber eine signifikant höhere immunologische Reaktivität als bei der Kontrollgruppen festgestellt. Es ist bekannt, dass gerade unbehandelte oder ungenügend behandelte Streptokokkeninfektionen heute am oftesten den Vorgänger der Febris rheumatica darstellen, was auch in unserem Kollektiv beobachtet werden konnte. Unsere Beobachtung stimmt darum auch in diesem Falle mit der praktischen Erfahrung überein. In diesem Kollektiv war aber der Umstand bedeutsam, dass auch bei den übrigen Mitgliedern die Reaktivität gegenüber der Kontrollgruppe leicht erhöht war. Es scheint, dass diese Erhöhung mit der Beobachtung anderer Autoren, die einen wesentlichen Einfluss des ungünstigen Arbeitsmilieus feststellten (4), im Einklang steht. Es ist jedoch fraglich, ob der Einfluss des feuchten Arbeitsmilieus direkt oder nur durch Disposition für Katarrhe der oberen Luftwege an der Entwicklung der Hyperreaktivität teilnehmen kann. Es ist aber nicht ausgeschlossen, dass diese leichte Hyperreaktivität durch latente Streptokokkenkontakte in der Epidemie verursacht werden konnte.

In Zukunft erscheint es also als notwendig, den Einfluss sowohl des bakteriellen Faktors als auch der übrigen exogenen Faktoren auf die Dynamik der immunologischen Reaktivität zu verfolgen. Es wäre auch nötig, die Rolle der wiederholten Streptokokkeninfektion und den Bestand der gewonnenen Hyperreaktivität zu bestimmen, um die Teilnahme der Hyperreaktivität in der Pathogenese des akuten Gelenkrheumatismus zu definieren.

Zusammenfassung

Die Autoren haben die immunologische Reaktivität in der Rekonvaleszenz der behandelten und unbehandelten Streptokokkeninfektion untersucht und mit der Reaktivität der Kontrollpersonen verglichen. In der Rekonvaleszenz der unbehandelten Streptokokkeninfektion haben sie eine signifikante Hyperreaktivität gefunden, während in der Gruppe der mit Penicillin behandelten Streptokokkeninfektion die Werte der Reaktivität normal waren.

The significance of streptococcal infection for the immunological reactivity of the macro-organism.

The authors have examined the immunological reactivity of convalescents after treated and untreated streptococcal infections respectively, and compared it with the reactivity of control persons. They found a significant hyperreactivity in convalescents after untreated streptococcal infection, while the group of persons whose streptococcal infections had been treated with penicillin, showed normal reactivity values.

La signification de l'infection streptococcique pour la réactivité immunologique du macro-organisme.

Les auteurs se sont livrés à une étude comparative de la réactivité immunologique chez des convalescents relevant d'une infection streptococcique traitée ou non traitée, par rapport à la réactivité observée chez des sujets-témoins normaux. Ils ont constaté que les convalescents dont l'infection streptococcique n'avait fait l'objet d'aucun traitement présentaient une hyperréactivité marquée, alors que ceux qui avaient été traités par la pénicilline, présentaient une réactivité normale.

Importancia de la infección estreptocócica en relación con la reactividad immunológica del macroorganismo.

Los autores han investigado la reactividad inmunológica en la convalecencia de infecciones estreptocócicas tratadas y no tratadas, comparándola con la reactividad de sujetos control. En la convalecencia de las infecciones estreptocócicas no tratadas han observado una hiperreactividad significativa, mientras que en el grupo de infecciones estreptocócicas tratadas con penicilina los valores de la reactividad eran normales.

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From the Pediatric Clinic of Karolinska Institutet at Karolinska Sjukhuset, Stockholm

Respiratory Studies in Children

II. Lung Volumes in Symptom-free Asthmatic Children, 6–14 Years of Age[1]

by SVEN KRAEPELIEN, INGA ENGSTRÖM and PETTER KARLBERG

Prominent among respiratory diseases in childhood is bronchial asthma, the incidence of which seems to be increasing. During the chronic course of the disease, in which acute attacks alternate with more or less asymptomatic intervals, decisions regarding therapy and prognosis must be made for each separate case. Essential questions are how rapidly irreversible pathological anatomical changes may arise. Tests of respiratory function may aid in evaluating and treating children with asthma. The object of the present study, and of later ones which will be published as a series in this journal, was to investigate the lung function of children with bronchial asthma during symptom-free periods. This paper will present a study of lung volumes.

Changes of lung volumes in asymptomatic adults with asthma have been shown earlier (2, 7, 8). Among the few studies published about asthmatic children is that of Lukas (1951), who investigated six symptom-free asthmatic children in the 11–15 years age range (9) and found an increased residual volume and an increased ratio of residual volume to total lung capacity. Bates (1952) examined 13 asthmatic patients aged 12–19 years, with only four below 15 years of age (1), and found an increased functional residual capacity compared to the values obtained in 14 healthy individuals in the same age range. Nine of the asthmatic patients were, however, not quite free of symptoms.

Definitions and Nomenclature

For a graphic presentation of the lung volumes with their definitions the reader is referred to Fig. 1 of the authors' earlier paper (6). The nomenclature is that proposed by a committee headed by J. R. Pappenheimer (10).

[1] Aided by a grant from the Swedish Association against Tuberculosis and Other Social Diseases.

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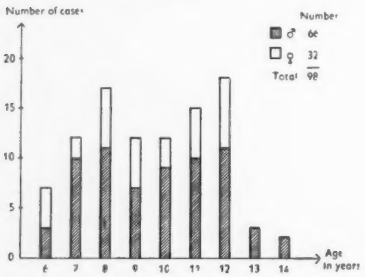

Fig. 1. Age and sex distribution of the children studied.

Material

The children studied attended the Allergy Outpatient Clinic or were patients of the Allergy Ward at the Pediatric Clinic of Karolinska sjukhuset. Examinations of asthmatic children were made only when they had been entirely free from symptoms and had received no symptomatic treatment during at least the past three days. Among the latter only those children were excluded who had been observed to be especially anxious and therefore probably not cooperative. On this basis 98 children were selected. They were in the 6–14 year age range; 66 were boys, and 32 girls. Thus the sex distribution chanced to be that normally encountered in asthmatic children (Fig. 1). The children's physical development was judged from the Broman, Dahlberg & Lichtenstein normal values for Swedish children (3). These apply to the relation of length to age and weight to length. For these two relationships all of the 98 children in the present study fell within the 95 per cent confidence limits. The severity of the disease was judged according to the frequency of asthma attacks (Table 1).

TABLE 1

Classification of asthma.

Group	Course	No. of cases
I	Mild asthma with less than 5 short attacks a year	39
II	Moderately severe asthma with 5–10 attacks a year	25
III	Severe asthma with more than 10 attacks a year, or prolonged status asthmaticus	34
Total		98

Methods

A closed circuit system with helium as the test gas was used for the determination of the functional residual capacity (V_{FRC}), as described in a previous report (6). In addition to the V_{FRC}, the expiratory reserve volume (V_{ER}) and the inspiratory capacity (V_{IC}) were also measured. From these values, the residual volume (V_R), vital capacity (V_{VC}) and the total lung capacity (V_{TLC}) were calculated. All volumes were corrected to BTPS.

As in the earlier study of healthy children, a duplicate determination was made in each case after a 10–15 minutes rest. Technically satisfactory double tests were obtained in 86 of the 98 cases studied.

Random Error of the Method

The random error of the method for each lung volume determined has been calculated from the differences between the duplicate determinations, according to Dahlberg (5), the results being given in Table 2. The coefficients of variation for the different items are slightly higher in the present series than those obtained in healthy children (6). The explanation may be that asthmatic children are subject to greater instability.

TABLE 2

The random error of the method of determining different lung volumes in symptom-free asthmatic children.

	V_{FRC}	V_{ER}	V_R	V_{IC}	V_{VC}
Number of duplicate determinations	86	86	86	86	86
Mean difference (d), liters	+0.0044	−0.0019	+0.0048	+0.0520	+0.0534
Standard deviation of the differences (σ_d), liters	±0.1192	±0.0758	±0.1286	±0.1054	±0.1021
Error in the mean difference (ε_d), liters	±0.0129	±0.0082	±0.0139	±0.0114	±0.0110
$t = d/\varepsilon_d$	0.34	0.23	0.35	4.63	4.85
P	>0.05	>0.05	>0.05	<0.001	<0.001
Standard deviation in an individual determination (σ_x), liters	±0.0843	±0.0536	±0.0909	±0.0745	±0.0722
Mean of all duplicate determinations ($\bar{x}$), liters	1.58	0.66	0.92	1.64	2.30
Coefficient of variation $(\sigma_x \times 100)/\bar{x}$, %	±5.34	±8.12	±9.88	±4.54	±3.14

Results

(With statistical treatment)

In the following analysis the boys and girls are not studied separately since there was such a small difference between the values obtained for

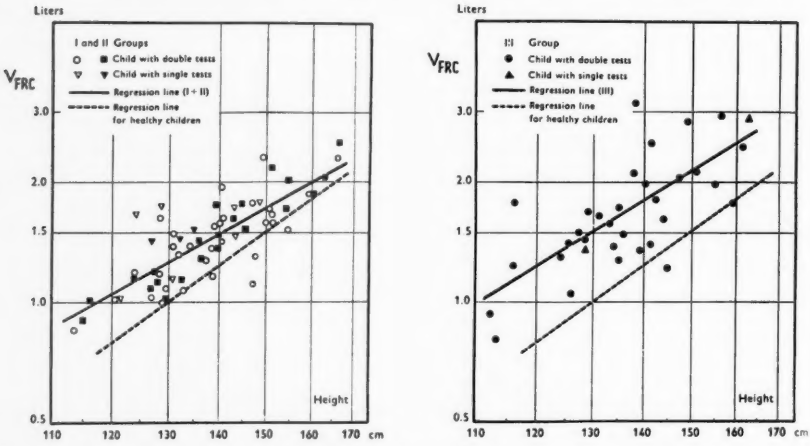

Fig. 2. The functional residual capacity (V_{FRC}) in relation to body height on a double logarithmic plot. The calculated regression lines are drawn. The regression line for the authors' material of healthy children is also shown.

healthy boys and girls. As in the study of healthy children, the lung volumes have been related to body height representing the body size. The individual results for V_{FRC}, V_R, V_{VC} and V_{TLC} have been plotted on a double logarithmic scale (Figs. 2–5). For each lung subdivision, Groups I and II are plotted together on one chart and Group III separately on another. The ratios V_{FRC}/V_{TLC} and V_R/V_{TLC} in relation to age, are shown in Figs. 6

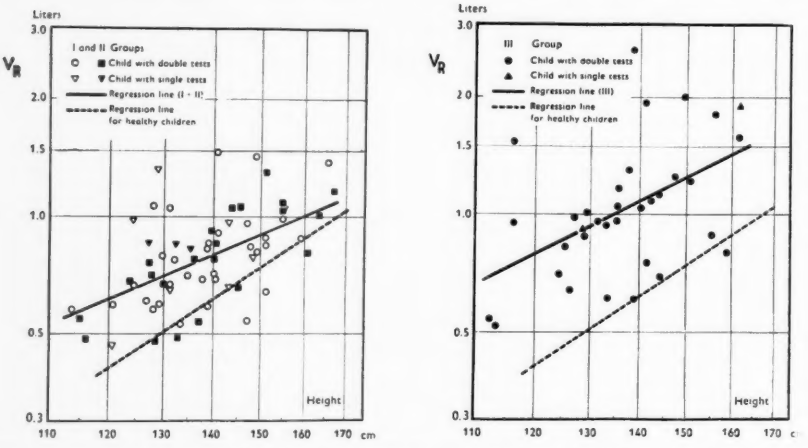

Fig. 3. The residual volume (V_R) in relation to body height on a double logarithmic plot. The calculated regression lines are drawn. The regression line for the authors' material of healthy children is also shown.

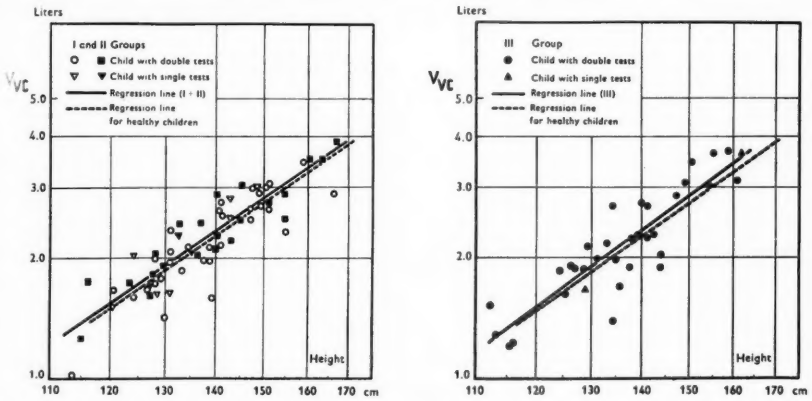

Fig. 4. The vital capacity (V_{VC}) in relation to body height on a double logarithmic plot. The calculated regression lines are drawn. The regression line for the authors' material of healthy children is also shown.

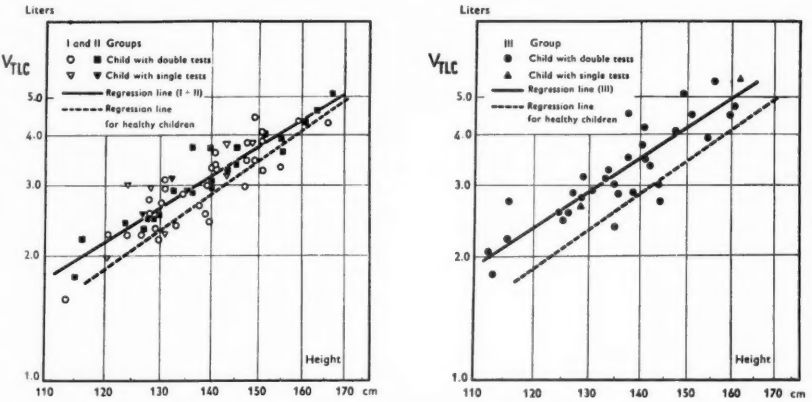

Fig. 5. The total lung capacity (V_{TLC}) in relation to body height on a double logarithmic plot. The calculated regression lines are drawn. The regression line for the authors' material of healthy children is also shown.

and 7. It was evident from the charts that there was no significant difference between Groups I and II, and therefore these two groups have been treated statistically as one.

Calculation of the regression equation for each lung subdivision has been performed in the same manner as in the earlier study of healthy children. Regression lines have been calculated for each lung subdivision and ratio and are drawn (Figs. 2–7) together with the comparable regression lines for healthy children. For most of these volumes and volume ratios the charts

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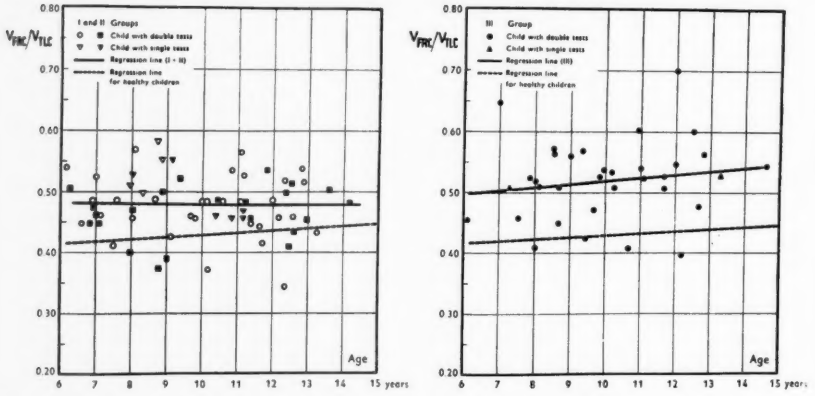

Fig. 6. The ratio of functional residual capacity to total lung capacity (V_{FRC}/V_{TLC}) in relation to age. The regression lines are drawn. The regression line for the authors' material of healthy children is also shown.

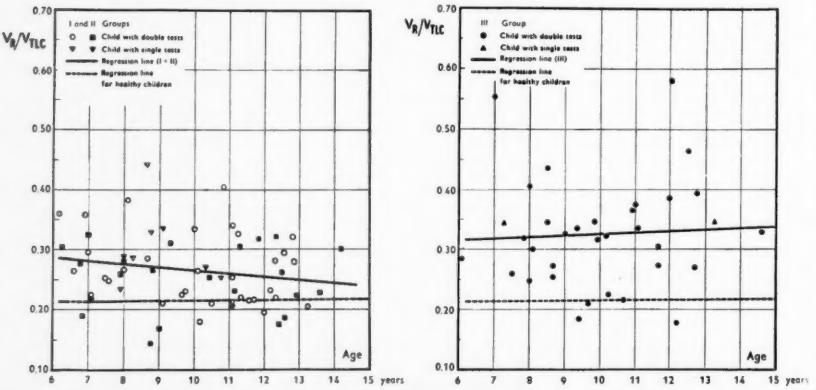

Fig. 7. The ratio of residual volume to total lung capacity (V_R/V_{TLC}) in relation to age. The regression lines are drawn. The regression line for the authors' material of healthy children is also shown.

show a difference between the asthmatic and the healthy children, and between the combined Group I plus II and Group III. The significance of these differences has been tested by analysis of covariance (Table 3). The V_{FRC}, V_R and V_{TLC}, and the ratios V_{FRC}/V_{TLC} and V_R/V_{TLC}, are in all groups of asthmatics significantly higher than the values found in healthy children. In these tests on lung functions there is also a significant statistical difference between Group I plus II and Group III. No difference, however, has been found in the V_{VC} of asthmatic children of all groups and the healthy children.

TABLE 3

Analysis of covariance. Comparison of the regression lines found for symptom-free asthmatic children and for the healthy children.

Regression lines for	Difference between slopes	Distance between regression lines
Group I plus II and Healthy		
V_{FRC}	$0.05 > P > 0.01$	$P < 0.001$
V_R	$0.05 > P > 0.01$	$P < 0.001$
V_{VC}	$P > 0.2$	$P > 0.2$
V_{TLC}	$0.2 > P > 0.05$	$P < 0.001$
V_{FRC}/V_{TLC}	$0.2 > P > 0.05$	$P < 0.001$
V_R/V_{TLC}	$0.2 > P > 0.05$	$P < 0.001$
Group III and Healthy		
V_{FRC}	$P > 0.2$	$P < 0.001$
V_R	$P > 0.2$	$P < 0.001$
V_{VC}	$P > 0.2$	$P > 0.2$
V_{TLC}	$P > 0.2$	$P < 0.001$
V_{FRC}/V_{TLC}	$P > 0.2$	$P < 0.001$
V_R/V_{TLC}	$P > 0.2$	$P < 0.001$
Group I plus II and Group III		
V_{FRC}	$P > 0.2$	$P < 0.001$
V_R	$P > 0.2$	$P < 0.001$
V_{VC}	$P > 0.2$	$P > 0.2$
V_{TLC}	$P > 0.2$	$P < 0.001$
V_{FRC}/V_{TLC}	$P > 0.2$	$0.01 > P > 0.001$
V_R/V_{TLC}	$P > 0.2$	$P < 0.001$

Discussion

A characteristic feature of asthma bronchiale is its intermittent course with periods of acute attacks between clinically free intervals. The acute attack is caused by a bronchial obstruction and is characterized by difficulty of expiration. This leads to a successive increase in the residual volume of the lung, followed by a rise in the resting expiratory level and diminished vital capacity. In the initial stage of the disease the bronchial obstruction and resultant hyperinflation are not likely to be more than temporary. But after repeated attacks, or after lengthy periods of even slightly obstructed expiration, the hyperinflation may become permanent and an emphysema may develop. An emphysema of this kind is defined as "a pathological condition of the lung characterized by reduction or loss of elastic fibers, ruptured alveolar septa and decrease in the pulmonary capillary bed" (4).

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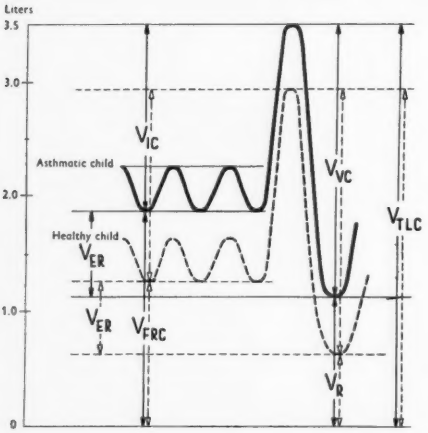

Fig. 8. The mean values of the different lung volumes calculated from the regression lines for 140 cm tall healthy and Group III asthmatic children. No consideration is taken into the timing of the breathing.

All degrees of changes are encountered, of course, from a temporary hyperinflation caused by acute bronchial obstruction to a continuous hyperinflation in the case of a permanent emphysema. The variations can be due to the frequency and intensity of the asthmatic attacks, whether the lung is able to return to or approach its normal function in the asymptomatic intervals, and the duration of the disease. Constitution factors may also be of some importance.

A number of studies of lung volumes in adult asthmatics have revealed chronic changes even during symptom-free intervals. In growing children two possibilities are conceivable: either that they are more susceptible than adults to changed conditions of ventilation and therefore become more readily hyperinflated after a small number of attacks, or that the elasticity of the lung tissue and the growth processes reduce the risk of irreversible changes.

The present study has shown that children with bronchial asthma likewise give signs of hyperinflation of the lungs during symptomfree intervals. By freedom from symptoms we mean that they are untroubled by dyspnoea and are entirely free from rhonchi. As would be expected, when the children are grouped according to frequency of attacks, the group with the most frequent attacks (Group III) has shown the greatest changes; the same changes occur in the other groups, but are of less magnitude.

The general trend of the changes in lung volumes is shown schematically in Fig. 8. The mean values of the different lung volumes in a 140 cm child have been calculated from the regression lines for healthy children and Group III asthmatics. It is thanks to the close correlation between lung volume and body size in children that this comparison has been possible

V_{FRC} is increased, which means that the lung is hyperinflated during quiet breathing. V_R, too, is increased, indicating that the lung is hyperinflated even after maximal expiration. V_{VC}, on the other hand, does not deviate significantly from the values found in healthy children; this may be due in part to our technique, since we have used two-stage capacity, which may reduce the effect of the bronchial obstruction. We chose this technique in order to attain better standardization and a more representative measure of the static lung volumes.

Since the vital capacity is normal despite the increased residual volume, the increase in total capacity of the lungs is of the same magnitude as the increase in residual volume.

The equal increases in V_R, V_{FRC} and V_{TLC} are thus a sign of hyperinflation of the lungs. But it is not possible to determine to what extent the hyperinflation is due to a permanent emphysema and to what extent it is due solely to a functional bronchial obstruction.

The hyperinflation, indicated by an elevated resting expiratory level, leads to an expansion of the thorax, hampering the maximal forced expiration, reflected in an increased residual volume. It is probable that, during normal development, the alveoli become successively more dilated. The lung of an asthmatic child can therefore be said to have accelerated the otherwise normal development, so that parenchymal damage of the lung should not be necessarily expected to be the cause of the changes in lung volume. This is not entirely true, however, since in such case one should have expected proportional increase in all lung volumes, and thus constant ratios as well. This has not happened; no increase is found in V_{VC}, and the ratios are higher, indicating a changed pulmonary function and not merely an accelerated development.

Nor does the finding of a significant relationship between changes in lung volume and frequency of attacks, when comparing the various groups, enable a definite statement to be made regarding the etiology of these changes. If attacks are frequent, the parenchymal changes may be expected to arise more quickly, but it is also possible that the last attack occurred so shortly before the examination that the hyperinflation during the attack has not had time to recede completely. The determination of the static lung volumes before and after administration of bronchodilator drugs may provide better possibilities of solving this problem.

The significant changes are found for the asthmatic children as a whole. However, as Figs. 2–7 show, there are in all three groups individual cases in which the lung volumes are similar to those of healthy children. Thus the clinical classification does not always coincide with the lung function changes in individual cases. The changes in lung volumes may be affected

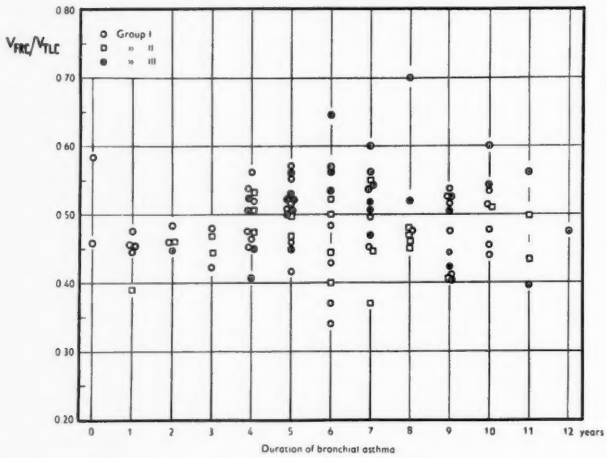

Fig. 9. The ratio of functional residual capacity to total lung capacity (V_{FRC}/V_{TLC}) in relation to the duration of bronchial asthma and to the three groups of different frequency of attacks.

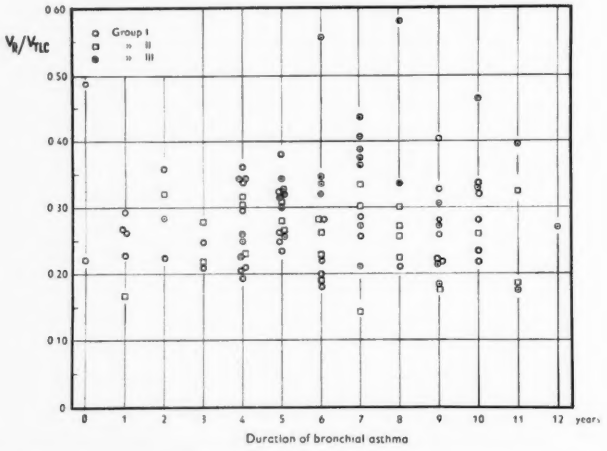

Fig. 10. The ratio of residual volume to total lung capacity (V_R/V_{TLC}) in relation to the duration of bronchial asthma and to the three groups of different frequency of attacks.

not only by the frequency of the asthma attacks but also by the duration of the disease. To evaluate the influence of the duration, the ratios V_{FRC}/V_{TLC} and V_R/V_{TLC}, which are almost independent of age, have been plotted in Figs. 9 and 10 against the duration of disease with different symbols to describe the varying frequency of attacks. The charts show a predominance

of high ratios between four and seven years in duration. However, with longer continuance of the disease there is less frequency of high ratios than of normal ratios, indicating possibly that some of the cases are in remission.

Further informations about the lung volume changes with time are necessary to judge whether the accuracy of the clinical classification may be improved by taking into account also the duration of the disease. Longitudinal studies are in progress.

Summary

1. The lung volume relationships in 98 asthmatic children (66 boys and 32 girls) aged 6–14 years were studied during asymptomatic intervals. The patients have been classified in three groups according to the frequency of asthmatic attacks.

2. The functional residual capacity (V_{FRC}) was measured by a closed circuit method using helium as the test gas.

3. The inspiratory capacity (V_{IC}) and expiratory reserve volume (V_{ER}) were determined by spirometry in connection with the determination of V_{FRC}. The vital capacity (V_{VC}) and the residual volume (V_R) were calculated from these three lung volumes.

4. The different lung volumes in relation to height and the ratios V_{FRC}/V_{TLC} and V_R/V_{TLC} in relation to age have been compared with those for healthy children. V_{FRC}, V_R and V_{TLC}, and both the ratios, are significantly higher than those in healthy children, indicating a hyperinflation of the lungs. The changes in lung volume are related to the frequency of attacks. No differences in V_{VC} were found. The origin of the lung volume changes is discussed.

5. The changes in lung volume are found in the asthmatic children as a whole. In all three groups, however, there are some individual patients with lung volumes similar to those found in healthy children.

6. The possibility of increasing the accuracy of the clinical classification by taking into account not only the frequency of attacks but also the duration of the disease is discussed.

Etude de la respiration chez l'enfant. II. Volumes pulmonaires chez les enfants asthmatiques âgés de 6 à 14 ans, sans symptômes respiratoires.

1. Les relations réciproques entre les volumes pulmonaires chez 98 enfants asthmatiques (66 garçons et 32 filles) âgés de 6 à 14 ans, ont été étudiées au cours de périodes pendant lesquelles aucun symptome n'était présent. Les patients ont été classés en trois groupes, selon la fréquence des crises d'asthme.

2. La capacité résiduelle fonctionnelle (V_{FRC}) a été mesurée à l'aide d'un système clos où l'hélium est utilisé comme gaz témoin.

3. La capacité inspiratoire (V_{IC}) et le volume expiratoire de réserve (V_{ER}) ont été mesurés à l'aide d'un spiromètre, conjointement à la mesure de V_{FRC}. La capacité vitale (V_{VC}) et le volume résiduel (V_R) ont été calculés sur la base de ces trois mesures.

4. La relation entre ces différents volumes et la taille d'une part, la relation entre les rapports V_{FRC}/V_{TLC} et V_R/V_{TLC} et l'âge d'autre part ont été comparées aux valeurs obtenues chez les enfants normaux. V_{FRC}, V_R, V_{TLC} et les deux relations mentionnées ci-dessus sont, d'une manière significative, plus élevés que chez l'enfant normal : ceci

traduit l'état d'expansion exagérée des poumons. L'importance des modifications du volume pulmonaire est proportionnelle à la fréquence des crises d'asthme. Aucune différence entre les valeurs de V_{VC} n'a été trouvée. L'étiologie de ces modifications du volume pulmonaire est discutée par les auteurs.

5. Ces modifications du volume pulmonaire ont été trouvées sur des groupes d'enfants asthmatiques. Cependant dans les trois groupes, certains patients montrent des valeurs identiques à celles trouvées chez l'enfant normal.

6. Les auteurs discutent la possibilité d'augmenter la précision de la classification clinique en tenant compte non seulement de la fréquence des crises, mais aussi de la durée de l'affection.

Atmungsstudien bei Kindern. II. Die Lungenvolumina bei symptomfreien Asthmakindern im Alter von 6–14 Jahren.

1. Die Lungenvolumina und ihr Verhältnis zueinander wurden bei 98 Kindern mit Asthma bronchiale (66 Jungen und 32 Mädchen) zwischen 6 und 14 Jahren in anfallsfreien Zeitabschnitten bestimmt. Je nach Häufigkeit der Asthmaanfälle wurden die Kinder in drei Gruppen eingeteilt.

2. Die funktionelle Residualluft (V_{FRC}) wurde mit Hilfe eines geschlossenen Kreislaufsystems mit Helium als Testgas gemessen.

3. Die inspiratorische Kapazität (V_{IC}) (=Atemluft + Komplementärluft) und die (expiratorische) Reserveluft (V_{ER}) wurden durch Spirometrie im Zusammenhang mit der funktionellen Residualluft (V_{FRC}) bestimmt. Die Vitalkapazität (V_{VC}) und die Residualluft (V_R) wurden an Hand dieser Lungenvolumina berechnet.

4. Die verschiedenen Lungenvolumina in ihrer Beziehung zur Länge und das Verhältnis V_{FRC}/V_{TLC} sowie V_R/V_{TLC} in Beziehung zum Alter wurden mit entsprechenden Werten für gesunde Kinder verglichen. V_{FRC}, V_R, V_{TLC} sowie V_{FRC}/V_{TLC} und V_R/V_{TLC} sind signifikant höher als bei gesunden Kindern und sprechen für eine Überblähung der Lungen. Das Ausmass der Lungenvolumänderungen steht in Beziehung zur Anfallsfrequenz. Für V_{VC} wurden keine Unterschiede gefunden. Die Ursache für die Veränderungen der Lungenvolumina wird erörtert.

5. Die Lungenvolumänderungen finden sich bei sämtlichen Asthmakindern. In allen drei Gruppen sind jedoch einige Einzelfälle, deren Lungenvolumina sich denen gesunder Kinder annähern.

6. Die Möglichkeit wird erörtert, die Genauigkeit der klinischen Einteilung zu erhöhen, indem man nicht nur der Anfallshäufigkeit, sondern auch der Krankheitsdauer Rechnung trägt.

Estudio de la respiración en la infancia. II. Volúmenes pulmonares en los niños asmáticos de 6 a 14 años de edad, sin síntomas respiratorios.

1. Las relaciones recíprocas entre los volúmenes pulmonares en 98 niños asmáticos (66 varones y 32 mujeres) de 6 a 14 años de edad, han sido estudiados en el curso de periodos durante los cuales, ningún síntoma estaba presente. Los pacientes fueron clasificados en 3 grupos, según la frecuencia de las crisis asmáticas.

2. La capacidad residual funcional (V_{FRC}) fué medida con la ayuda de un sistema cerrado, donde el helio fué utilizado como gas testigo.

3. La capacidad inspiratoria (V_{IC}) y el volumen expiratorio de reserva (V_{ER}) fueron medidos con la ayuda de un espirómetro, conjuntamente a la medida de V_{FRC}. La capacidad vital (V_{VC}) y el volumen residual (V_R) fueron calculados sobre la base de esas tres medidas.

4. La relación entre esos diferentes volumenes y la talla, por un lado, y las relaciones entre las proporciones V_{FRC}/V_{TLC} y V_R/V_{TLC} y la edad, por otro lado han sido comparadas a los valores obtenidos en los niños normales. V_{FRC}, V_{TLC}, V_R y las dos relaciones mencionadas anteriormente, son de una manera significativa, más elevadas que en los niños normales: lo que traduce un estado de expansión exagerada de los pulmones. Los cambios en el volumen pulmonar están en relación directa a la frecuencia de las crisis asmáticas. No fué encontrada ninguna diferencia entre los valores de V_{VC}. La etiología de esas modificaciones del volumen pulmonar es discutida por los autores.

5. Esas modificaciones del volumen pulmonar han sido encontradas en grupos de niños asmáticos. En los 3 grupos, sin embargo, algunos pacientes mostraron valores idénticos a los encontrados en niños normales.

6. Los autores discuten la posibilidad de aumentar la precisión de la clasificación clínica, teniendo en cuenta no solamente la frecuencia de las crisis asmáticas, sino también la duración de la afección.

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Respiratory Studies in Children

III. Lung Volumes in Children with Prurigo Besnier (Atopic Dermatitis)[1]

by SVEN KRAEPELIEN

In an earlier paper in this series of investigations Kraepelien *et al.* (4) showed by means of spirometry that changes occurred in the static lung volume of symptom-free asthmatic children and that the degree of change was correlated to the frequency of the asthmatic attacks the child had suffered during the past year. The functional residual capacity and the residual volume had increased, signifying the presence of hyperinflation of the lungs. Since the conditions of even mildly affected asthmatic children often differ from those of healthy children, the question arises whether allergics in general, in view of their special constitution, differ in their lung physiology from healthy individuals, and, if so, whether the fact is reflected in changes in lung volume even when there is no history of respiratory symptoms. That such may be the case is suggested by the fact that eczema patients manifest a high family incidence of asthma (5) and that roughly 50 per cent of children who have had hospital treatment for infantile eczema later develop asthma (3 and 6). To throw some light on this question, a study was made of a group of eczema children who had never had asthmatic symptoms.

Definitions, Nomenclature, Methods, and Random Errors of the Methods

Definitions, nomenclature, methods and random errors have been given in earlier papers by the author and coworkers (2 and 4).

Material

The material consisted of 16 children with prurigo Besnier (atopic dermatitis) aged 7–13 years (8 boys and 8 girls). These children were taken from a follow-up group consisting of all children with prurigo Besnier admitted

[1] Aided by a grant from the Swedish Association against Tuberculosis and Other Social Diseases.

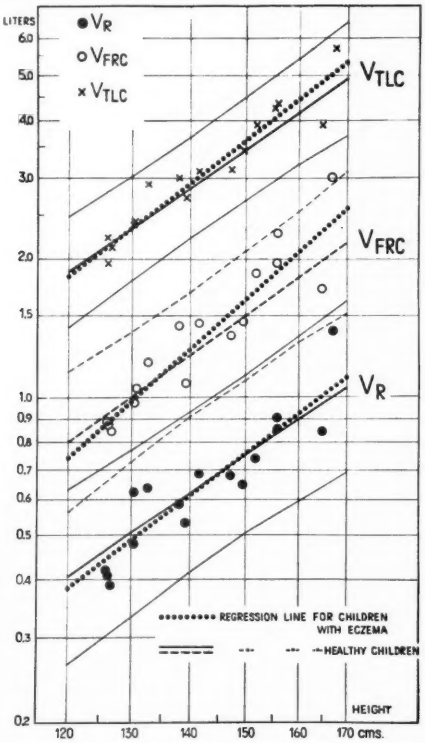

Fig. 1. The total lung capacity (V_{TLC}), the functional residual capacity (V_{FRC}) and the residual volume (V_R) in relation to body height on a double logarithmic plot. The calculated regression lines are drawn. The regression lines with 95 per cent confidence intervals for healthy children are also shown.

to the Department of Dermatology of Karolinska Sjukhuset during the years 1948–1956. The age distribution is shown in Fig. 2. An attempt was made to obtain a uniform age distribution within the particular age range, but otherwise the selection was as random as possible. The physical development of all the children conformed with the normal values for Swedish children given by Broman, Dahlberg & Lichtenstein, based on age, height and weight (1). The children had had their eczema for various periods, ranging from 6 to 13 years, and it had varied in intensity and extent at different times. When examined, 14 children displayed a typical prurigo Besnier, while in two the skin was intact. Three of the children had earlier had urticaria, but none had had asthmatic symptoms in any form. In the three days before the examination no child had received any medicamental therapy apart from local application of ointment.

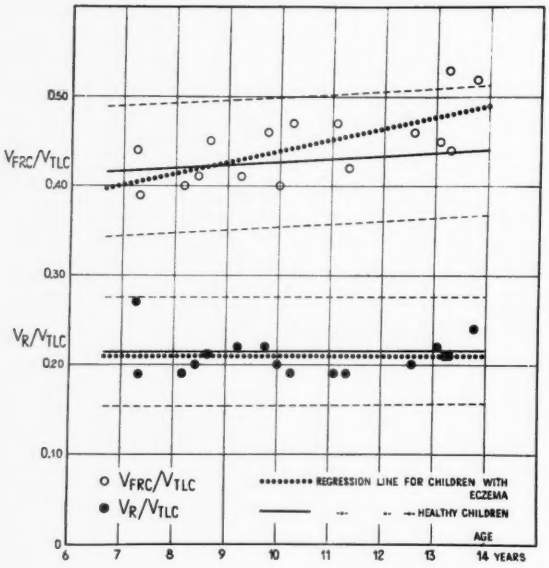

Fig. 2. The ratios of functional residual capacity to total capacity (V_{FRC}/V_{TLC}) and residual volume to total lung capacity (V_R/V_{TLC}) in relation to age. The calculated regression lines are drawn. The regression lines with 95 per cent confidence intervals for healthy children are also shown.

Results

As in earlier investigations in healthy children and in symptom-free asthmatic children the lung volumes has been correlated to the body height (2, 4). Since earlier investigations had revealed so little difference between boys and girls, no distinction was made between the sexes. The individual results as regards functional residual capacity (V_{FRC}), residual volume (V_R) and total lung capacity (V_{TLC}) were plotted on a double logarithmic scale (Fig. 1). The regression lines with 95 per cent confidence intervals for the lung volumes in healthy children are shown in the same chart. The ratios V_{FRC}/V_{TLC} and V_R/V_{TLC} in relation to age are plotted in Fig. 2, in which the regression lines with 95 per cent confidence intervals for the ratios in healthy children are also drawn. (The mean value for V_{FRC}/V_{TLC} in healthy children equals 0.429 ± 0.0372, and for V_R/V_{TLC} 0.217 ± 0.0295. Thus the 95 per cent confidence interval for V_{FRC}/V_{TLC} is 0.355–0.503, and for V_R/V_{TLC} 0.158–0.276.)

As seen from Fig. 1, the values of V_{FRC}, V_R and V_{TLC} in the individual cases are very well grouped around the respective regression lines for healthy children. All values except one for V_{FRC} are within 95 per cent confidence intervals. The same conformity is found for the ratios V_{FRC}/V_{TLC} and V_R/V_{TLC}, but as regards V_{FRC}/V_{TLC} two eczema children come rather outside the 95 per cent confidence intervals (0.52 and 0.53): see Fig. 2.

A statistical analysis was made to determine the probability whether this randomly selected group of eczema children differs from healthy children in lung volume. Regression calculations were made in the same way as in earlier investigations of healthy children. The regression lines have been drawn on Figs. 1 and 2. The same calculation has been made for the vital capacity (V_{VC}). The probability of difference in slope and distance between regression lines found for the eczema children and healthy children was calculated by covariance analysis (see Table 1). A significant difference was found only for two lines: for V_{FRC} as regards the slope, and for the ratio V_{FRC}/V_{TLC} as regards slope and distance. Otherwise no statistically significant deviations from the conditions in healthy children were observed.

TABLE 1

Analysis of covariance. Comparison of the regression lines found for the eczema children and for the healthy children.

Regression lines for	Difference between slopes	Distance between regression lines
V_{FRC}	$0.01 > P > 0.001$	$P > 0.2$
V_R	$0.2 > P > 0.05$	$P > 0.2$
V_{VC}	$P > 0.2$	$P > 0.2$
V_{TLC}	$P > 0.2$	$P > 0.2$
V_{FRC}/V_{TLC}	$0.01 > P > 0.001$	$0.01 > P > 0.001$
V_R/V_{TLC}	$P > 0.2$	$P > 0.2$

Discussion

Among the sixteen cases examined only one case, in one of the volumes investigated (V_{FRC}), was outside the 95 per cent confidence interval for healthy children. Since this child happened to be the tallest in the group, it had a big influence on the slope of the calculated regression line for the material regarded as a group. The same case naturally had a high V_{FRC}/V_{TLC} ratio as well. Among the older children there was another with high V_{FRC}/V_{TLC}, which influenced the distance between regression lines for eczema children and healthy children. In these two cases, however, V_R, V_{TLC} and the ratio V_R/V_{TLC} lie completely within the variations found among healthy children, so that the two children do not show lung changes typical of those found in symptom-free asthmatic children. The remaining children have shown very close conformity with healthy children, as regards all lung volumes and ratios. The size of the material was therefore considered sufficient for the purpose.

The investigation shows that allergic children with skin lesions but no asthmatic symptoms as a rule do not differ in static lung volume from healthy children in the way as the symptom-free asthmatic children do. Consequently there are no grounds for suggesting that solely an allergic constitution might be the cause of the changes in lung volume found in symptom-free asthmatic children.

Summary

1. The lung volume relationships were studied in sixteen children with prurigo Besnier (atopic dermatitis), but showing no respiratory symptoms whatsoever. Eight were girls and eight boys, the ages being 7–13 years.

2. The study shows that fifteen of the eczema children do not deviate from the conditions in healthy children. Only one child differs from healthy children, but not in the way as the symptom-free asthmatic children do.

3. There are no grounds for stating that solely an allergic constitution as such would cause changes in lung volume.

Etude de la respiration chez l'enfant. III. Volumes pulmonaires des enfants présentant des lésions de Prurigo de Besnier (atopic dermatitis).

1. Les diverses composantes du volume pulmonaire et leurs relations réciproques ont été étudiées chez seize enfants, présentant des lésions de Prurigo de Besnier (atopic dermatitis), sans aucun symptôme respiratoire. Le groupe étudié était composé de huit garçons et huit filles, âgés de 7 à 13 ans.

2. Chez quinze de ces enfants eczémateux, les valeurs obtenues sont identiques à celles trouvées chez l'enfant normal. Un seul enfant s'écarte des valeurs normales; mais non comme s'en écartent les enfants asthmatiques sans symptômes respiratoires.

3. Rien ne permet de conclure que la constitution allergique, en soi, modifie les volumes du poumon.

Atmungsstudien bei Kindern. III. Die Lungenvolumina bei Kindern mit Prurigo Besnier (Neurodermitis circumscripta).

1. Die verschiedenen Lungenvolumina und ihr Verhältnis zueinander wurden bei 16 Kindern mit Prurigo Besnier (Neurodermitis circumscripta) aber ohne Symptome von Seiten des Atemapparates bestimmt. Acht waren Mädchen und acht Jungen im Alter von 7–13 Jahren.

2. Fünfzehn der Ekzemkinder zeigen keine Abweichung von den Verhältnissen bei gesunden Kindern. Nur ein Kind unterscheidet sich von Gesunden, jedoch nicht in derselben Weise wie symptomfreie Asthmakinder.

3. Es besteht kein Anhaltspunkt dafür, dass lediglich eine allergische Konstitution als solche Änderungen des Lungenvolumens mit sich führt.

Estudio de la respiración en la infancia. III. Volumenes pulmonares en la infancia con Prurigo de Besnier (Dermatitis atópica).

1. Los diversos componentes del volumen pulmonar y sus relaciones recíprocas fueron estudiados en 16 niños que presentaban lesiones de Prurigo de Besnier (atopi-

dermatitis). El grupo estudiado estaba compuesto de 8 varones y 8 mujeres, de 7 a 13 años de edad.

2. En 15 de esos niños eczematosos, los valores obtenidos son idénticos a los encontrados en los niños normales. Un solo niño dió valores alejados de los normales, pero no como lo hacen los niños asmáticos sin síntomas respiratorios.

3. Nada permite conduir, que la constitución alérgica, por si misma, modifique los volumenes pulmonares.

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Intermittent Positive Pressure Respiration in Infants with Poliomyelitis

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A notable advance in the treatment of the "life-threatening" complications of poliomyelitis has been the use of intermittent positive pressure respiration, either by manual ventilation or by the use of positive pressure respirators (Lassen, 1953).

Despite the wide experience gained, there have been few reports on the use of positive pressure respiration in infants. Of 345 cases of life-threatening poliomyelitis encountered in the Copenhagen epidemic of 1952, only 6 were less than one year old (Pedersen *et al.*, 1956). Five children with 3 survivals were included in 89 respirator cases treated in Sweden in 1953 (d'Avignon *et al.*, 1956). Fatal cases in a 9-year-old boy (Hay, 1954) and a 10-month-old infant (Lawes & Harries, 1956) have been reported.

In addition, these reports have been published from centers, where equipment, nursing and laboratory arrangements are at a high standard. Many of the countries which deal with the respiratory management of poliomyelitis in infants are not in a position to maintain the high standard of facilities and nursing considered essential for successful therapy.

Our experience of positive pressure respiration in 12 infants, ranging in age from one half to three years and treated in a general paediatric department is presented here, in the hope that it may be of use to others who may have to face the same problem.

Indications for Treatment

Our indications for treatment fell into two classes:

(1) *Bulbo-spinal paralysis with respiratory muscle involvement.*—In these cases postural drainage alone, or the use of the tank respirator alone, would not be successful. To avoid death from underventilation, on the one hand or "drowning in secretions" on the other hand, positive pressure respiration was instituted, allowing us to maintain a clear air-way and satisfactory gaseous exchange via the tracheotomy. Seven infants were of this group.

(2) "*Wet-respiratory*" *cases.*—This concept has been well described by Lassen (1956). In certain cases with respiratory paralysis, yet without bulbar palsy, sufficient secretions are present to cause trouble, despite frequent suctioning or tracheotomy within the iron lung. The only alternative is positive pressure respiration. Five infants fell into this category.

In practice there is little to differentiate between these two groups. Clinically, the distinction may be difficult in infants, since a "wet-respiratory" case may have difficulty in swallowing, due to the accumulated secretions, and an impression is gained that bulbar palsy co-exists. We consider that the indication for positive pressure respiration boils down to use on a patient with insufficient respiratory capacity and excess secretory activity.

In order to ensure that we were not carrying out an unnecessary form of treatment, the timing of our treatment was conservative. Eight cases were first treated in the iron lung with postural drainage, frequent suction and oxygen for varying periods. Only when it was obvious that their condition was deteriorating were they transferred to positive pressure respirator. These patients acted as a form of control for themselves. The remarkable difference between the hyper-pyrexic, cyanotic, sweating, dyspnoeic, restless child in the iron lung, and the quieter, pink, dry child on manual ventilation, was evident within a few hours, and amply justified the change of therapy.

Attempts to return the patient to the iron lung after a few days on bag ventilation, were unsuccessful. Only after the condition stabilised could three children be returned with ease to the iron lung, with the tracheotomy still present. The transference from one form of artificial respiration to the other caused no disturbance. It is only the presence of secretions that causes trouble when the patient is in the iron lung, and calls for intermittent positive pressure respiration instead.

Problems in the Management of Infants

In order to assess treatment in the respiratory management of infants with poliomyelitis, it is important to appreciate the problems specially existing in this age group.

(1) Tank respiration is difficult to adjust to the respiratory rate of young children and infants. "The respiratory cycling of infants is an exacting and painstaking task" (O'Brien *et al.*, 1954).

(2) Children tolerate hypoxia and carbon dioxide retention poorly. Early tracheotomy is indicated before shock due to hypoventilation sets in (Wisniki, 1955). On the other hand, in children it is easy to go over to hyperventilation, which, even if short, cannot be innocuous (Gozzano, 1955).

(3) "It is much easier to keep the pharynx of an adult or co-operative

adolescent clear of fluid, and therefore prevent obstruction of the air-way, than it is to do the same job for a small child or infant" (Hodes, 1955). This lack of co-operation applies to all aspects of management. Restlessness causing over-exertion, attempts to pull out a tracheotomy tube or an intravenous infusion, the difficulty in carrying out X-ray studies, blood-pressure measurements, and blood or urinary examinations, are all additional factors which enhance the therapeutic problem in the seriously-ill infant with poliomyelitis.

(4) With the smaller calibre of air passages in infants, secretions which are thick or purulent cause atelectasis with greater ease. The problem is aggravated by the tendency of infants to vomit, and to aspirate gastric contents.

Details of Procedure

(1) A high tracheotomy, carried out with local anaesthesia and bronchoscopic cover, was standard procedure. The importance of preceding bronchoscopy, or intubation, to allow for suction, oxygenation, and an unhurried operation, cannot be over-emphasised. In 2 cases operation was impossible until positive pressure respiration was carried out via the bronchoscope, after which tracheotomy was performed. It has also been found advisable to pass a gastric tube before the operation in order to avoid aspiration of gastric contents.

(2) An ordinary silver cannula was used and connected to the respiratory apparatus by a section of endotracheal tubing. "Cuffed tubes" have the advantage of preventing the entry of pharyngeal secretions into the bronchi, but were not used in our cases, as we did not have cuffed tubes available in the size required for infants. In addition, with the unskilled staff available, the danger of the tube slipping out, or slipping in too far, was undesirable. Cuffed tubes may also cause necrosis. Wislicki (1955) used a silver cannula from the onset in 2 adult cases with no untoward result. Finally, it was considered that the leakage of air around the silver cannula during positive pressure respiration helped to avoid excess inspiratory pressure, and acted as an aid in the elimination of carbon-dioxide during expiration.

(3) The *bag ventilation apparatus* in current use by anaesthetists was used in most cases (see diagram). Oxygen was used only for short emergency periods. For maintenance of respiration, air supplied by a compressor was used. As at one stage, 7 children were simultaneously receiving positive pressure respiration, a system of pipes and taps was set up by the local technical staff to ensure a controlled flow of air to each patient. A high flow of 8–10 litres per minute was given to allow for the removal of carbon-dioxide (Lassen, 1956) since soda-lime canisters were not available.

As mentioned above, the leakage of expired air around the cannula also aided in the removal of CO_2. The occasional CO_2 and (venous) blood pH estimations which were carried out showed normal values. Clinically, hypercapnia was noted only on few occasions.

(4) The use of a high flow of air into a tracheotomy made adequate humidification a problem. Copies of the humidifier described by Walley (1956) were not successful and the humidifier of Marshall & Spalding (1953) was not available. We were forced to resort to improvisation. A simple but adequate method of humidification was carried

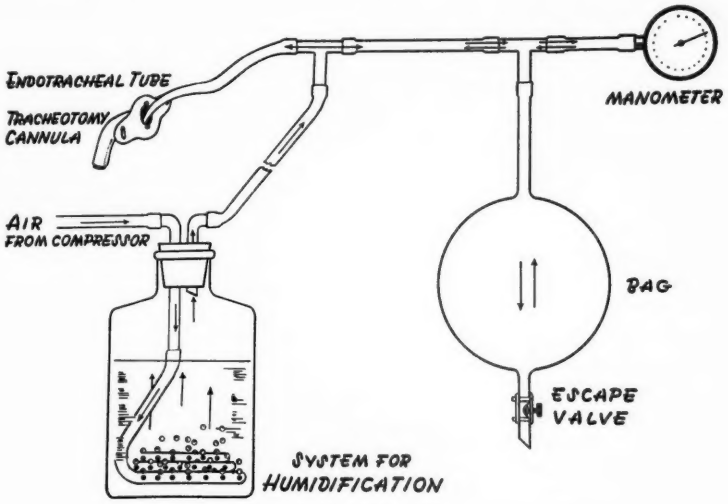

Fig. 1.

out by bubbling the air through two metres of polyethylene tubing, with numerous holes, which was set in a bell-jar of water. To ensure a satisfactory temperature, the bell-jar was placed in a large bucket of hot water with the temperature maintained at 37°C by frequent changes of water.

Despite all efforts, on occasion, respiratory insufficiency was noted due to thick, encrusted, sometimes infected secretions. To achieve efficient "lavage", small amounts of sterile saline solution were introduced into the trachea, and dispersed into the smaller bronchioles by a few positive respirations. Immediately after this, vigorous physiotherapy together with efficient tracheal suction usually resulted in the removal of these secretions.

(5) *Manual ventilation* based on a short inspiratory phase, up to a pressure of about 20 cm of water, and a prolonged expiratory phase to avoid circulatory upset, was used. Rate of ventilation was about 30 per minute. The majority of the personnel were unskilled, and included some of the parents of the patients, as well as medical students from the Hebrew University, Jerusalem. An Engström positive pressure respirator was available, and used with success on one patient, and during a stable period on another patient. There have been many testimonies to the value of this machine (Lassen, 1956; Fanconi, 1955). However, it was our impression that the marked variability in respiratory and secretional "status" which was present in these infants, made it difficult to commence treatment with any form of mechanical positive pressure respiration.

(6) *Nutritional requirements* in all except two cases, during the first 24–48 hours were given intravenously in addition to plasma and nor-adrenaline, when necessary. In two cases, intravenous fluids were given up to six days after the onset of positive pressure respiration. The danger of intravenous fluid administration in the period after operation, as stressed by Ibsen (1956), does not seem a great one in infants. Following the period of infusion, tube-feeding by means of a permanent polyethylene

Fig. 2. Close-up to show details of connection between bag ventilation apparatus and ordinary tracheotomy cannula, by means of endo-tracheal tubing. Note also use of indwelling polyethylene catheter for gastric feeds.

gastric tube was carried out, until bulbar paralysis had passed off, or secretions had diminished to a sufficient extent to allow normal feeding. As part of the maintenance regime, blood transfusions were given frequently.

(7) *Lung physiotherapy* (postural drainage, tapping, "squeezing", etc.) combined with frequent, gentle suction from the nose and mouth and via the tube, was regarded as of primary importance (Andersson, 1956), especially considering that the non-utilisation of a cuffed tube allowed pharyngeal secretions to spill over into the bronchi and lungs. Since skilled physiotherapists were not available, the treatment was carried out by the junior medical personnel working in shifts during the three months' period, thus also ensuring the constant presence of a doctor in the ward.

(8) To prevent infection, catheters were kept in a sterile saline solution and full antibiotic cover was given. Our efforts met with only partial success. Two patients died of secondary pneumonia. Swabs taken regularly from the nose, pharynx and trachea showed positive cultures within a few days of tracheotomy in nearly all cases. The organisms grown, *Staph. aureus*, *B. proteus*, *B. pyocyaneus*, were similar to those found in Sweden (Tunevall, 1956). Wide spectrum antibiotics were given in accordance with the sensitivity of the organisms. Penicillin and streptomycin solutions were also used intra-tracheally to combat infection.

(9) Through sheer necessity, laboratory procedures were kept to a minimum without any obvious deleterious effect. Regular X-ray studies, blood counts, urinary pH and chloride estimations, and bacteriological cultures were however carried out on all pa-

ients. Blood urea, proteins and electrolyte levels were investigated from time to time in most of the patients.

(10) *Decannulation.* This was achieved in 5 patients. The period from cessation of intermittent positive pressure respiration until decannulation ranged from 35 to 63 days with an average of 50 days. Two patients with fairly good coughing ability were decannulated without any difficulty. In the remaining cases, due to diaphragmatic paralysis, a poor cough, or the presence of granulation tissue, decannulation represented a critical period. Despite the intensification of the physio-therapeutic regime, continued postural drainage, and frequent naso-pharyngeal suction, secretions tended to accumulate, due to the poor coughing ability of these patients. It was found necessary therefore to leave a small rubber catheter "in situ" in the tracheotomy for 24–36 hours to enable tracheal suction to be carried out. In this manner the patients were tided over this critical and important period.

Following decannulation, one patient had recurrent bouts of fever and atelectasis, while another patient required treatment in the iron lung during short periods of respiratory insufficiency.

(11) Peripheral paralysis was present in all cases and physiotherapy for the limbs was carried out as well. Seven of our twelve patients were tetraplegic.

Results and Complications

The results of treatment are summarised in the table.

The period of positive pressure respiration ranged from one day to 138 days with an average of 40 days. In some cases although return of muscular function occurred, it was necessary to continue manual ventilation due to the presence of atelectasis or infected, non-functioning areas in the lungs.

Five patients out of the twelve survived. Of these, one patient with severe encephalo-bulbar-respiratory involvement remained in a state of "decerebration". Four patients (one bulbar-respiratory, 3 "wet-respiratory") were transferred to a rehabilitation center, or discharged home.

Complications occurred in all patients. It is possible that the incidence of complications may have been less had there been no treatment in the iron lung beforehand in eight of the twelve patients. Pneumonia was severe enough to cause death in two patients. Seven patients developed atelectasis at least once. Two of these required bronchoscopy to achieve clearing of the atelectatic area. In the others intensive physiotherapy was sufficient for this purpose. In one patient with tetraplegia, atelectasis was terminal after six months on continual artificial respiration.

Circulatory failure immediately after tracheotomy, requiring nor-adrenaline infusion, occurred in two patients. In two other patients, during the course of treatment, sudden cessation of respiration was accompanied by absent heart-sounds. Intra-cardiac adrenaline administered immediately resulted in the return of heart-sounds. However, one of these patients deve-

TABLE 1

An analysis of 12 cases of positive pressure respiration in infants.

No.	Age yrs.	Sex	Type[a]	Preceding "iron lung" therapy	I.P.P.R. (no. days)	Complications	Outcome
1	1½	M	B-R	6 hrs	17	Atelectasis	Paraplegia: Rehab. centre
2	1½	M	W-R	< 12 hrs	19	Purulent bronchitis	Paraplegia: Rehab. centre
3	½	M	B-R	–	58	Atelectasis; gastro-enteritis; cardiac standstill	Died (long sinus thrombosis) Cerebral atrophy
4	1½	F	W-R	24 hrs	16	Sudden death	Died (pulm. oedema, pneumonia)
5	1½	M	B-R	< 6 hrs	138	Atelectasis	Died (atelectasis, pneumonia)
6	¾	F	B-R	–	1	Circulatory failure	Died (atelectasis)
7	3	F	W-R	16 hrs	90+	Atelectasis	Died (peri-bronchial fibrosis)
8	2	M	W-R	8 hrs	43	Atelectasis, enteritis, mumps, measles	Paraplegia sup.: Rehab. centre
9	½	F	E-B-R	–	17	Cardiac standstill, convulsions; atelectasis; pneumonia	Died (atelectasis, pneumonia)
10	1½	F	B-R	< 6 hrs	27	Pneumonia	Died (mid-brain haem., pneumonia)
11	2	M	E-B-R	–	12	Coma, retention, convulsions, gastric dilatation	Decerebrate state
12	1	F	W-R	2 days	42	Atelectasis, enteritis	Discharged home

[a] B-R = bulbar-respiratory; W-R = "wet-respiratory"; E-B-R = encephalo-bulbar-respiratory.

loped convulsions and the other showed gross cerebral atrophy at post-mortem examination.

Gastric dilatation, gastro-enteritis, urinary retention, mumps and measles complete the list of complications encountered.

Pathological Findings

All the seven patients who died were submitted to post-mortem examination.

The neuro-pathological findings in the bulbar-spinal group were marked by their intensity, with haemorrhages into the brain-stem and vacuolisation

of the anterior horn cells. Recovery in these cases seemed to be extremely unlikely.

One patient, who underwent an episode of cardiac standstill, died after 101 days in the ward with a terminal gastro-enteritis. A fresh thrombus was found in the superior longitudinal sinus in addition to marked cerebral atrophy.

In five patients respiratory complications were considered as the major factor in causing death, viz. pneumonia (2), atelectasis (2), pulmonary oedema (1).

In another patient, who died after 180 days of continual artificial respiration, marked fibrosis around the pulmonary arterials and bronchioles was found throughout both lung fields. This finding has not been noted by others. Its significance is obscure, although it may be related to hypoxia, or the possible development of pulmonary hypertension after prolonged artificial respiration.

Discussion

It is essential to view these cases against the general background of hospital admissions for poliomyelitis, and the overall mortality.

Among the 270 patients admitted in 1956, in addition to the seven deaths amongst the group treated with positive pressure respiration, 12 other children died, and all but one were submitted to post-mortem examination. These deaths can be grouped as follows:

(1) Two moribund infants died within 40 minutes of admission.

(2) Two children died within 12 hours of admission due to a fulminating ascending paralysis and pulmonary oedema.

(3) One case died with suppurative pneumonia and myocarditis after being admitted with pneumonia.

(4) Three children died at the time of tracheotomy which was being done for the purpose of positive pressure respiration. Death was due to extensive atelectasis. One patient vomited during the operation, while another child was operated upon without preceding bronchoscopy.

(5) Five children died while in the iron lung, as a result of aspiration or atelectasis. One patient was 4 weeks old, while in another bulbar involvement was found at autopsy.

In retrospect, some of these deaths were preventable and a reduction in mortality seems possible. Our experience with positive pressure respiration has given us a better understanding of the management of poliomyelitis in infancy. This can be deduced from the fact that the mortality rate has already been reduced, from the average of 14 % for the years 1953–1955 to a rate of 6 % in 1956, with the incidence and severity of cases encountered remaining unchanged. However, with increasing application of the principles learned

during the period under review, it is to be expected that the mortality rate will be further reduced.

It is felt that these principles of therapy are fairly simple. The prompt and correct start of treatment, avoidance of infection (as far as possible), effective lung physiotherapy, a bent for improvisation, and the setting up of a "twenty-four-hour regime" of therapy, are regarded as essential. With these requisites it seems possible to treat these patients in a general hospital with average personnel requirements, with the grim understanding, however, that a certain proportion of "hopeless" cases will always be present.

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Summary

Twelve infants suffering from life-threatening complications of poliomyelitis were treated with intermittent positive pressure respiration with 5 survivals. Indications for therapy, details of treatment, results and complications are discussed. Despite the special difficulties encountered in this age group, it is felt that effective treatment is possible within a general paediatric "set-up" and with simple equipment, provided that the basic principles are adhered to "24 hours a day".

Pression respiratoire intermittante positive chez les enfants avec poliomyélite.

12 enfants souffrant de complications de poliomyélite avec danger de mortalité furent traités avec une pression respiratoire intermittante positive, dont 5 ont survécu. On discute les indications pour la thérapeutique, les détails du traitement, les résultats et les complications. Malgré les difficultés particulières rencontrées dans ce groupe d'âge, on a l'impression qu'un traitement efficace est possible dans le cadre de la pédiatrie générale et avec un équipement simple, à condition que les principes de base soient adhérés « 24 heures sur 24 heures ».

Intermittierende, positive Druckbeatmung bei Kindern mit Poliomyelitis.

12 Kinder mit lebensbedrohenden Komplikationen bei Poliomyelitis wurden mit intermittierender positiver Druckbeatmung behandelt. Resultat: 5 Überlebende. Indikationen für die Therapie, Einzelheiten betreffend Behandlung, Resultate und Komplikationen wurden diskutiert. Trotz der bei dieser Altersgruppe speziell auftretenden Schwierigkeiten hat man die Empfindung, dass eine wirkungsvolle Behandlung im Rahmen eines allgemeinen erzieherischen „Set-up" und mit einfacher Ausrüstung möglich ist, vorausgesetzt, dass die Richtlinien dem „24-Stunden-Tag" angepasst sind.

Respiración mediante presión positiva intermitente en niños afectos de poliomielitis.

Doce niños afectos de complicaciones poliomielíticas graves fueron tratados con respiración mediante presión positiva intermitente, obteniéndose la sobrevivencia de cinco de ellos. Se discuten las indicaciones del tratamiento, sus detalles, resultados y complicaciones. A pesar de las especiales dificultades con que se tropezó, se tiene el convencimiento de que es posible llevar a cabo un tratamiento efectivo con una "organización" pediátrica general y con un equipo simple, teniendo en cuenta que un factor básico es la asistencia constante del enfermo.

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Familial Juvenile Nephronophthisis

by G. HACKZELL and C. LUNDMARK

Introduction

In the early 1950's Fanconi *et al.* (1951) described a syndrome observed in two families in which most of the children had either died or were suffering from renal diseases of the same type.

In one of the families, four of the five children had fallen ill, only the youngest still being healthy. The four had become victims of the disease at the age of 2–3 years, and three died when 5½–6 years old. The fourth child was still alive and 4 years old at the last examination. The youngest child was 3 years old and in good health.

Also the other family had five children. The first and fourth child were healthy, the others ill. The healthy children had reached an age of 19 and 10 years, respectively. The rest had fallen ill at different ages, from 2 to 6 years. The two eldest of the sick children had died at about 15 years of age, the youngest at 8½ years.

The course of the disease was very similar in these cases. Apart from a general lack of appetite, the primary symptoms had been a slowly beginning polyuria, polydipsia and nycturia. The urinary quantities were fairly large and the specific gravity of the urine was low. In concentration tests, low values were obtained, and gradually a complete isosthenuria developed. In the urinary sediment, occasionally one or two red and white blood corpuscles were ascertained, otherwise nothing pathologic was noted. Generally no protein was found in the urine, sometimes insignificant albuminuria. The blood pressure was not at all increased, or but slightly so. Thus, clinical indications of cystopyelitis or nephritis were entirely lacking. A certain tendency to hypoglycemia appeared rather early, as well as to hyperelectrolytemia. Several of the children had had unexplained convulsions in their anamnesis. The phosphorus value was fairly high, while the calcium value was rather low, as also that of the alkaline reserve. The NPN showed increa-

singly higher values and the serum values in other respects indicated a progressing renal failure. The children died of uremia.

In 1952, Hackzell reported a family in which two of the children had renal diseases that entirely corresponded to those described by Fanconi *et al.* In connection with that report, Enell (1952) mentioned that he had observed a similar syndrome in two children in another family. In 1956, Zetterström (to be published) described a similar case from the Pediatric Clinic of Karolinska Sjukhuset. As far as we know, the literature lacks further descriptions of such cases. As two children in either of the families reported by Hackzell and Enell, respectively, had died, and a complete patho-anatomic examination of three of the cases had been performed, it was considered worth while to give an account of the observations.

Case Reports

Family I

Case Karin.—The patient was the eldest in a family of 4 children. Normal development. Of children's diseases she had only had the measles. On the whole healthy until almost 7 years old, when she fell ill with a bronchial catarrh and a temperature lasting for a few days. A private doctor gave sulfa treatment. At a check-up after the infection the same doctor observed that the examination of the urine gave negative findings. However, rather marked anemia was also ascertained. The patient had earlier shown a certain tendency to anemia. She was feeling in rather good spirits for half a year, but the blood values increased only insignificantly in spite of iron medicine. Urinary quantities remarkably large. She was admitted to hospital owing to iron-resistant anemia when 7 years and 7 months old. Physical examination without remark. Blood pressure 120/70. Urinary status: traces of albumin. Nothing pathologic in sediment. Urinary quantities approx. 1½ litres. The Volhard water test showed unsatisfactory dilution and concentration. Hb 50 %, NPN 95 mg% to 180 mg%. Retrograde pyelography revealed contracted renal pelvis on the right side and a clumsy renal pelvis on the left. The case was interpreted as a chronic glomerulonephritis in combination with anemia. She was discharged after a fortnight. The parents, who were informed of the unfavourable prognosis, consulted another doctor and the patient was admitted to another hospital after 5 weeks. The blood pressure was then 115/65. Weight 22 kg. In the urine: traces of albumin. Sediment without remark. Specific gravity 1.012. Hb 46 %, red blood corpuscles 2.14 mill., white cells 4400. Differential count without remark. Blood chlorides 291 mg%, plasma protein 7%, blood calcium 10.1 mg%. Sedimentation rate 45 mm. Abdominal survey by means of radiography showed kidneys of normal size with distinct contours. Radiography of the lungs and heart without remark. Eyegrounds without remark. Her blood values fell still further being, on one occasion, as low as 30% Hb, 1.5 mill. red blood corpuscles. She was given repeated blood transfusions, which caused temporary increase in blood values. She gradually grew worse and died of uremia when 8 years and 5 months old. No post-mortem examination was performed.

Case Ulla.—The patient was the second, in a family of 4 children. Normal development. Of children's diseases she had had parotitis, pertussis, and varicella. Bronchial

catarrh at about 4 years old. Otherwise on the whole healthy, apart from slight tendency to obstipation. At about 7 years old, she began to drink excessively and also had large urinary quantities. To begin with, a private doctor was consulted, who ascertained that the urine was without remark. Urography, however, disclosed very unsatisfactory excretion. She was admitted to hospital for the first time at the age of 7 years and 7 months. The following was noted from physical examination: weight 26.6 kg, normal bodily structure. No edema. Physically without remark. Blood pressure 110/70. Slight strabismus of the left eye. Urine contained no albumin and sediment showed nothing pathologic. Urinary quantities approx. 1.6 litres per 24-hour period. Specific gravities constantly at about 1.012–1.014. pH 5 in the urine. The Volhard water test revealed unsatisfactory dilution to 1.010 and concentration to 1.017. NPN 52 mg%. Sedimentation rate 28 mm. Hb 10.7 g%, red blood corpuscles 3.3 mill., white 7.200, differential count normal. Total protein in serum 7.9 %, 4.9 % of which was albumin, total cholesterol 216 mg%, calcium 12.3 mg%, phosphorus 5 mg %, chlorides 370 mg%, sodium 318 mg%. Blood sugar (fasting value) 124 mg%. Alkaline reserve 41.6 vol.% CO_2. Urography did not show any visible excretion of contrast medium. Radiography of the skeleton revealed no decalcification. Eyegrounds without remark.

Her condition remained on the whole unchanged in the next two years, although the NPN value showed a tendency towards a slow increase. Now and then she felt fairly tired, but went to school as usual. Admitted to hospital again at the age of 8 years and 9 months. Physical examination showed no marked change. Weight 30 kg. Blood pressure 125/80. In the urine no albumin was found, the sediment showed no pathologic findings. Urinary quantities 1.3–1.6 litres per 24-hour period. Specific gravities fixed at about 1.010–1.011, also at the Volhard water test. The sedimentation rate 53 mm. NPN 72 mg%. Hb 10.7 g%, red blood corpuscles 3.7 mill. When the patient was 9 years and 9 months old, she had a sudden attack of convulsions with unconsciousness, probably in connection with an infection with fever. NPN was then 159 mg%, Hb 6.8 g %, red blood corpuscles 1.8 mill., blood calcium 10.7 mg%, serum phosphorus 6.7 mg%, alkaline reserve 31.5 vol.% CO_2. After a few days, she was in good spirits, but the NPN value rose to 186 mg%. The urinary quantities were much less. No edema. No vomiting. Blood pressure 110/70. Traces of albumin in the urine, the sediment without remark. The patient was at home for a month. In connection with a slight convulsion, she suddenly died at the age of 9 years and 10 months. On admission to the hospital she was already dead. Post-mortem examination, see below.

Family II

Case Einar.—The patient was the eldest in a family with three children. He had had the measles and parotitis. On the whole, normal development, though he had always been small and thin. When only 6 years old, he began to suffer from a violent thirst, and could sometimes drink as much as 3–4 litres per 24-hour period. At about the age of 9 years and a half, he was on two occasions subjected to general tonic convulsions, the first time lasting for 4 hours, the second time for 48 hours. He was admitted to hospital for examination at the age of 9 years and 11 months. The following was noted from the physical examination: strikingly small for his age, weight 23.6 kg, height 126 cm. Blood pressure 110/70. No edema. In the urine, no albumin was found, the sediment showed nothing pathologic. Specific gravity varied between 1.002 and 1.007. Urinary quantities ranged from 2.5 to 4 litres per 24-hour period. Hb 74 %, red blood corpuscles 4 mill., white 8000, differential count without remark. Serum chlorides 305 mg%, blood calcium 10.9 mg%, phosphorus 4.4 mg%. Alkaline reserve

61.5 vol. % CO_2. Blood sugar (fasting value) 86 mg %, glucose tolerance normal. Eye-grounds without remark. The case was interpreted as diabetes insipidus. Encephalography caused suspicion of suprasellar tumour, which was moreover later treated by roentgen rays. Treatment with posterior lobe hormone failed to bring about any reduction in the urinary quantities.

During the next 3 years his condition remained on the whole unchanged. On and off, tonic convulsions occurred of the same type as earlier. Examinations made in connection with these attacks showed normal blood calcium and phosphorus values. Galvanic excitability was increased on one or two occasions. Complete neurologic examinations gave no pathologic findings. Growth in height increasingly retarded. At about 14 years old the patient's condition deteriorated fairly rapidly and in that connection the urinary quantities decreased, the convulsions became more frequent and a slight albuminuria was found. He was re-admitted to hospital at the age of 14 years and 8 months, weighing 26 kg, and 135 cm tall. Blood pressure 120/80. Hb 55 %, red blood corpuscles 2.6 mill. Urinary quantities 0.5–2 litres per 24-hour period. Specific gravity 1.005–1.010. In the urine no albumin was found. The sediment showed nothing pathologic. Serum protein 9 %, 7.1 % of which was albumin, cholesterol 226 mg %. Blood calcium 9.2 mg %, phosphorus 6.5 mg %. Blood chlorides 308 mg %. Blood sugar (fasting value) 123–200 mg %. In the serum 263 mg % sodium and 18 mg % potassium. Sedimentation rate 45–79 mm. NPN increased rapidly for a couple of weeks from 46 mg % to 240 mg %. He died of uremia and acidosis after hospitalization for 3 weeks. It was not possible to verify the radiologic suspicion of a suprasellar tumour at autopsy, nor did a detailed examination of the brain disclose any notably pathologic changes. As regards other post-mortem findings, see below.

Case Marianne.—The patient was the third child. She had always been small and thin, but otherwise normally developed and on the whole healthy. She had had the measles and parotitis. At about 7 years old she began to suffer from increasing thirst and large urinary quantities. When she started school (at 7 years and 3 months) the urinary quantity was 2–3 litres per 24-hour period. She had nycturia 3–4 times. Gradually fatigue and loss of appetite were added. She was admitted to hospital the first time at the age of 8 years and 1 month. From physical examination: small, thin girl. Weight 20.6 kg. Height 122 cm. Blood pressure 125/80. In the urine, no albumin was found, the sediment without remark, specific gravity 1.008. Hb 11.6 g %, red blood corpuscles 3.64 mill., white 9.000, differential count without remark. Sedimentation rate 12 mm. NPN 29 mg %, serum chlorides 354 mg %. Blood sugar normal. Also in her case diabetes insipidus was suspected. Basal metabolism, glucose tolerance, encephalography, cranial radiography without remark. Radiography revealed a somewhat small sella turcica. Attempts with hypadrin injections and snuffing powder failed to bring about a change in the urinary quantities.

During the next two years her condition remained almost unchanged. Unsatisfactory increase of weight, bad appetite, often tired, slightly constipated. The patient was subjected to check-ups at the outpatient's department. She was re-admitted to the hospital at about 10 years old for examination on account of the fact that her brother's illness had been found to be a renal disease and not diabetes insipidus. From physical examination: weight 21.9 kg, height 126 cm. Urinary quantities still 2–3 litres. In the urine, no albumin, sediment without remark. Specific gravity 1.005. NPN 40 mg %. Sedimentation rate 31 mm. Intravenous urography disclosed no excretion whatever after 45 min. The investigation could not be completed because of the

TABLE 1

Own Cases. Essential clinical data.

Name (i) = ill (h) = healthy	Onset age	Death age	Urinary quantity litres	Spec. gravity	Albumin	Sediment	Maximum blood pressure	Non-protein nitrogen
				Family I				
Karin (i)	7	8	1.2–2.2	1.005–1.011	Traces	0	120	95–300
Ulla (i)	7	10	1.3–2.1	1.009–1.014	0	0	115	46–186
Kristina (h)	–	–	0.9	1.016	0	0	110	32
Agneta (h)	–	–	0.9	1.019	0	0	105	28
Erik (h)	–	–	–	–	–	–	–	–
				Family II				
Einar (i)	6	15	2–4	1.002–1.010	Small amounts	0	120	46–240
Marianne (i)	7	12	2–3	1.004–1.007	Traces	0	125	29–213
Lennart (h)	–	–	0.7	1.005–1.034	0	0	125	28

death of her brother and her parents wished to have her at home. She returned to the hospital 5 months later. She had become increasingly tired, but had gained in weight to 24.4 kg. She had no edema. Blood pressure 110/85. Urinary quantities about 3 litres per 24-hour period. Specific gravity between 1.004 and 1.007. Occasionally traces of albumin, the sediment without remark. NPN to begin with 100 mg%, but later again fell to 45 mg%. Blood calcium 11 mg%, phosphorus 5.54 mg%. In the serum, sodium equalled 358 mg%, potassium 22 mg%, chlorides 330 mg%, total cholesterol 214 mg%. Serum albumin and serum globulin without remark. Blood sugar (fasting value) 96 mg%. Volhard water test showed satisfactory excretion, but specific gravity fixed at between 1.005 and 1.006. Eyegrounds without remark. Retrograde pyelography without remark. Radiography of skeleton gave no noteworthy findings. Insulin, creatinin, para-aminohippuric acid clearances tests disclosed a marked reduction in glomerular filtration, but normal renal blood supply and all but normal tubular excretion. The patient's condition deteriorated gradually during the next 2 years. NPN increased and was sometimes as high as 200 mg%. She had pronounced tendency to anemia. She improved temporarily in connection with blood transfusions. During her last year of life she manifested, on and off, uremic symptoms with vomiting and headache. The urinary quantities gradually decreased. Blood pressure remained unchanged. Only insignificant protein. She died of uremia at the age of 12 years and 2 months. As regards post-mortem findings, see below.

As may be seen from Table 1 and from the complete case reports presented above, in the first family the two eldest children fell ill at about the age of 7 and died at the age of 8 and 10 years respectively. The other three children of that family, who are now 10, 8½ and 1 year, are still in good health. In

the other family, the two eldest children also fell ill at the age of about 6–7 years, and died at 15 and 12 years respectively. The youngest child of that family is still healthy and was, at the last examination, 7 years old. All the children fell victims of the disease in much the same way, showing a slight loss of appetite and fatigue. The most striking early symptom was increase of thirst and urinary quantities. Particularly in the second family, the urinary quantities had early become considerable, amounting to almost 4 litres. For that reason, at first diabetes insipidus was suspected. However, from the course of the disease, and after additional examinations, the opinion was arrived at that this was a case of primary renal disease. The specific gravity of the urine was low in all the cases, complete isosthenuria gradually being developed. In only one case was albumin ascertainable in measurable quantities, and that only for a short while. No pathologic findings in the urinary sediment were observed.

It also emerges from Table 1 that the blood pressure had been normal or but slightly elevated. In most of the cases a fairly pronounced anemia occurred. The NPN disclosed, to begin with, but a slight increase which, in the course of the disease, became more or less conspicuous. The children died of uremia.

Post-mortem examination

In the three cases subjected to autopsy, the renal changes were found to be practically identical, both from a macroscopic and histologic point of view. Accordingly, one description will serve for all these cases.

Macroscopically, the kidneys showed a far advanced state of atrophy with symmetric and diffuse reduction of the renal parenchyma. The capsule could be fairly easily detached. The consistency was firm and slightly tough. The surface was smooth in places, partly fine-granular. The colour of the cut surface was paler than usual and the outline was blurred with an indistinct boundary between the cortex and the medulla. The cortex was very thin. In one case, a minor cyst formation was observed, otherwise cysts were lacking, as well as deformed areas or large cicatrices.

Apart from a slight dilatation of the renal pelvis in two of the cases, there were no changes to be noted in the renal pelvis, ureters or urinary bladder. Thus, any signs of deformities in the urinary passages were entirely lacking.

At a *histologic examination* of the kidneys the following was observed:

The markedly reduced cortex contained numerous, altogether hyalinized glomerules, being most abundant in the external cortical zone. This total cicatricial transformation of the glomerules was preceded by an increase of the collagenous fibrils in Bowman's capsule, while the capillary loops were intact (Fig. 1A). Later the basal membrane of the capsular endothelium was greatly thickened and the collagenous fibres were hyalinized. The broad and sharply outlined capsule round an otherwise but slightly changed glomerulus was a very characteristic feature (Fig. 1B). When the process had advanced further, the capillary loops were more or less completely hyalinized together with the capsule (Fig. 1C). No signs of glomerulitis were found in the form of capsular exuda-

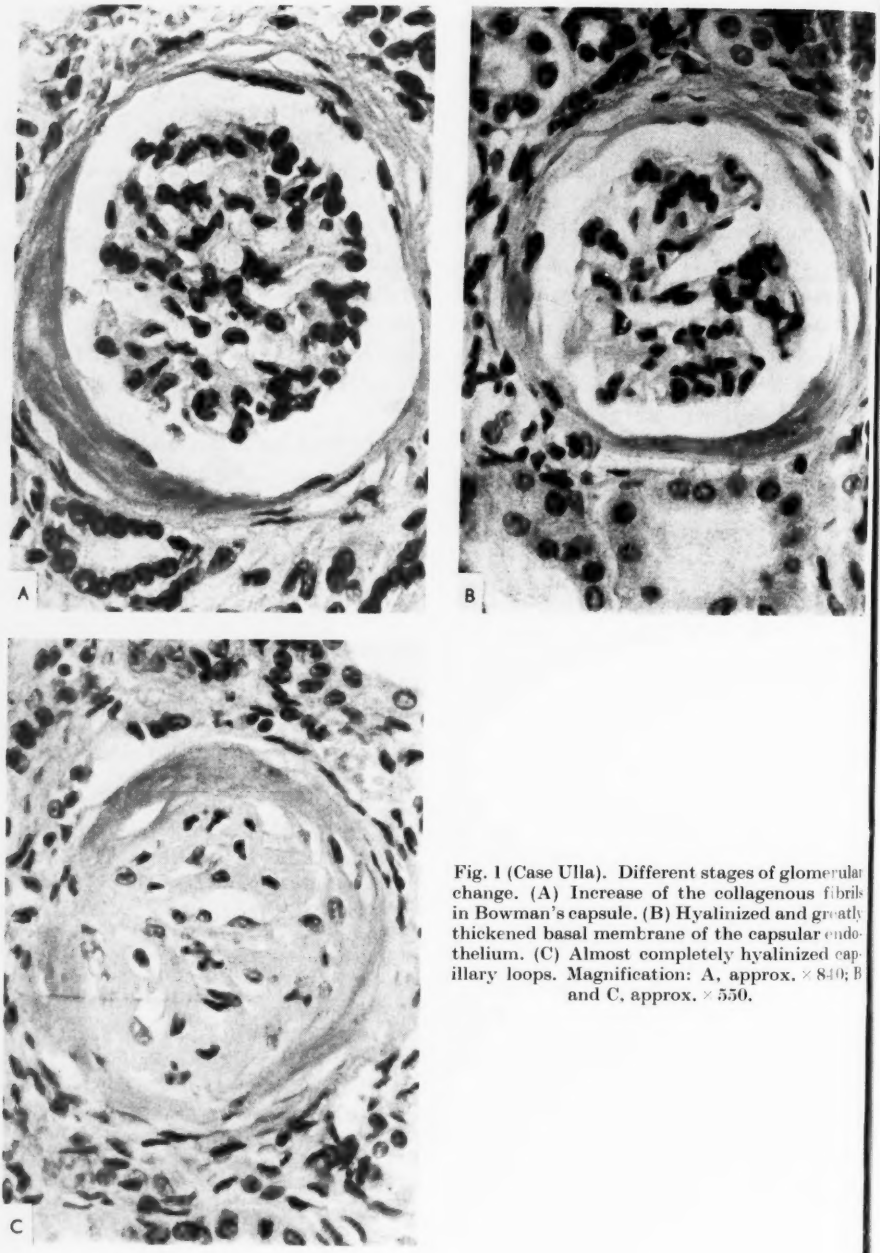

Fig. 1 (Case Ulla). Different stages of glomerular change. (A) Increase of the collagenous fibrils in Bowman's capsule. (B) Hyalinized and greatly thickened basal membrane of the capsular endothelium. (C) Almost completely hyalinized capillary loops. Magnification: A, approx. × 840; B and C, approx. × 550.

tion, inflammatory cells or an increase of the nuclear number in the capillary loops. Proliferation of the capsular endothelium was quite lacking. A small number of the numerous glomerules that were not engaged in the forementioned process were clearly hypertrophic.

The tubular part of the kidney was very severely damaged in its entirety. This was most evident in Henle's loops which were very atrophic and markedly disunited. However, hypertrophic and often dilated canals were to be seen in several places. The contrast between groups of atrophic and hypertrophic tubules was most apparent in the parts of the medullary pyramids situated nearest to the cortex and in the inner zone of the cortex which thereby obtained a segmented character (Fig. 2). Hardly any intact tubules were found and, when there were no other changes to be noted, degenerative injuries to the epithelial cells were observed with a fine-granular disintegration of the cytoplasm. Rather many canals were filled with homogeneous acidophilous masses. This gave the tissue a definitely thyroid-like appearance in places (Fig. 3). A large part of the basal membrane of the tubular epithelium was strongly thickened and often formed a broad sheath round the atrophic epithelium (Figs. 4 and 5). No accumulation of fat in the epithelial cells was observed. Staining to determine a metachromatically stainable substance gave negative results.

Between the remaining, more or less seriously injured nephrons the strongly developed interstitial connective tissue often appeared in powerful streaks. The collagenous fibrils were sometimes hyalinized, sometimes markedly separated, the latter probably owing to a pronounced edema. In several parts of the connective tissue, accumulations of lymphocytes and plasma cells occurred in varying quantities, being most abundant in the parts where the nephron atrophy was most conspicuous. Leukocytes were almost entirely lacking.

In one of the cases (Ulla) a number of small and medium-sized branches of the renal artery with moderately pronounced media hypertrophy were observed. Otherwise, no changes in the arteries or arterioles were found.

In the mucous membrane of the renal pelvis and in the adipose tissue of the renal sinus, no changes of any significance were ascertained, apart from a few isolated, small collections of lymphocytes.

As regards changes in other organs than the kidneys, only those of specific interest will be briefly referred to here. In two of the cases (Ulla and Einar), a distinct tendency was noted to lacunar bone resorption in the skeleton with the occurrence of osteoclasts at the edges of the irregularly decreased bone trabeculae. Further, all the cases disclosed a slight, diffuse hyperplasia of the parathyroid glands and a certain hyperplasia as well as an abundant accumulation of lipoid in the zona fascicularis of the adrenal cortex.

Summing up, concerning the renal changes observed in our cases, we have found them to be a manifestation of a symmetric and diffuse contraction with serious injury to the tubules and to the glomerules, though leaving numerous glomerules intact. The histologic picture is characterized by sheath-like basal membranes, a large number of more or less completely hyalinized glomerules, varying atrophic and hypertrophic tubules, areas with a thyroid-like appearance, a pronounced development of the interstitial connective tissue and, in places, accumulations of lymphocytes and plasma cells.

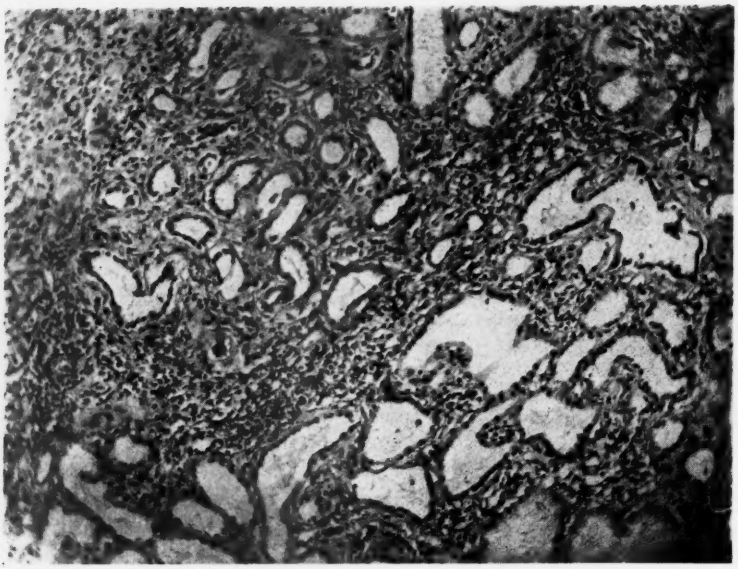

Fig. 2 (Case Ulla). A varying picture of atrophic and hypertrophic tubules. Magnification: approx. × 100.

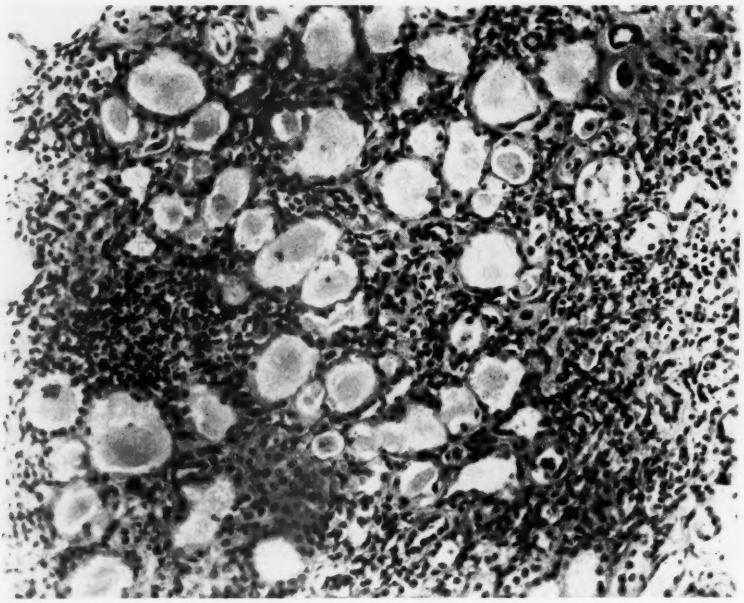

Fig. 3 (Case Einar). Area with a thyroid-like appearance. Magnification: approx. × 21(

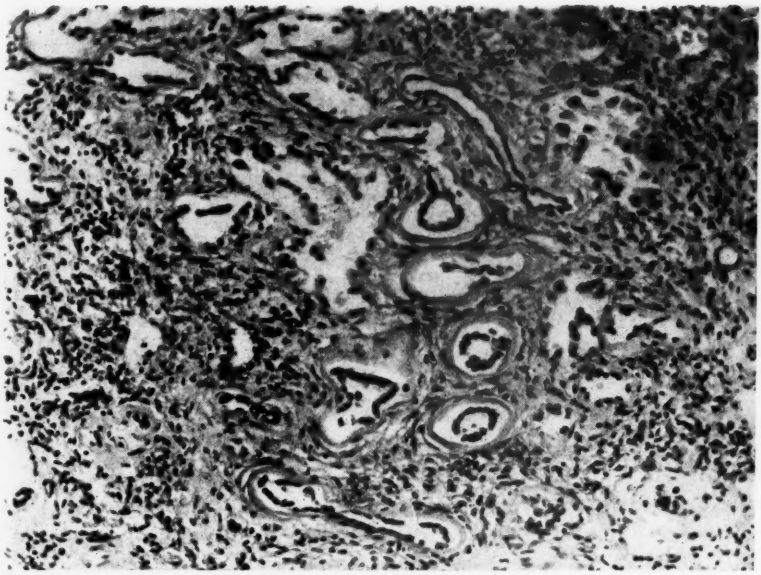

Fig. 4 (Case Einar). Thickened, sheath-like basal membranes round the atrophic tubules. Magnification: approx. × 165.

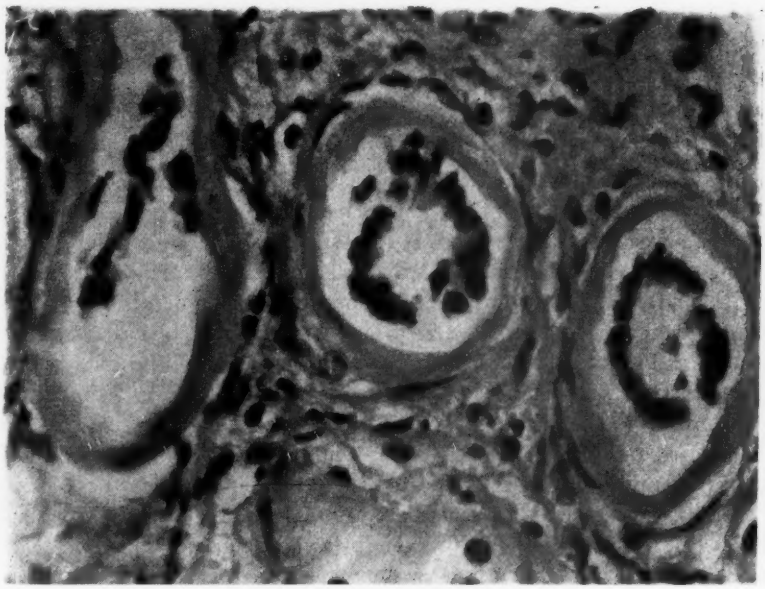

Fig. 5 (Case Einar). Detailed picture of Fig. 4. Magnification: approx. × 550.

Discussion

In the report made by Fanconi *et al.* of their cases, the renal change is described as a destruction of the renal parenchyma with hyalinization of the glomerular loops and basal membranes of the canals, as well as of atrophy, though to a lesser extent also hypertrophy, of the tubules. The description includes the occurrence of hyaline cylinders, an increase of the interstitial connective tissue and the occurrence of round cell infiltrations. Fanconi *et al.* state that, owing to the familial appearance of the disease and the fact that no deformities, basal metabolic disturbances, vascular changes or inflammatory processes have been ascertainable, the disease must be assumed to be due to a constitutional inferiority with an early destruction of the renal parenchyma. The aforementioned authors therefore decided to give the syndrome the name of "familiäre juvenile Nephronophthise".

As previously stated, no deformities in the urinary organs have been observed in our own autopsy cases, nor in those described by Fanconi *et al.* However, in one of our cases (in which no autopsy was performed), retrograde urography revealed a rather clumsy renal pelvis, on one side, and a small, shrunken renal pelvis, on the other. It is, of course, hard to say how this should be interpreted. In all likelihood, these changes appeared secondarily owing to a contraction of the kidneys. Otherwise the radiographic examinations failed to disclose any signs of deformity.

Intravenous urography disclosed a very deficient excretion. It was impossible to ascertain, by means of examinations of the urine and of the serum, whether the primary changes were situated in the glomerules or in the tubules. In one instance a simultaneous creatinin-insulin and para-aminohippuric acid clearance test was made, disclosing a marked decrease in the glomerular filtration and an almost normal tubular excretion. This does not seem to conform at all with the histologic pictures which, as mentioned earlier, showed very severe changes in the tubules. The extremely poor excretion of contrast medium at intravenous urography might, on the other hand, be in fair conformity with the pronounced changes noted in the tubules, where the greater part of the excretion of contrast media containing iodine is considered to take place. A disturbance in the fluid equilibrium has occurred at an early phase. This must no doubt be attributed to a deteriorated re-absorption in the distal sections of the tubules. The analyses of calcium, phosphorus, protein, chloride, sodium and potassium in the blood did not give any definite results, though a tendency was noted to an increase of the phosphorus values and a decrease of the calcium values, as in the cases described by Fanconi *et al.* Thus, the latter cases showed a striking resemblance to our own, both as regards anamnesis and clinical findings.

In our opinion, the histologic picture of the kidneys given in this paper differs in principle from that generally obtained in common types of contracted kidney, although certain histologic details show conformity. The patho-anatomic renal changes observed in our cases seem on the whole to correspond to that described by Fanconi *et al.*

The occurrence of lymphocytes and plasma cells in the renal tissue is interpreted by Fanconi *et al.* as a manifestation of a secondary resorption process in connection with the destruction of the renal parenchyma, and not as an inflammatory change in the actual sense of the word. We are inclined to share their opinion, particularly as such accumulations of cells are very often seen in various forms of renal atrophy, even those with a vascular origin.

The changes recorded in our cases in the parathyroid glands and in the skeleton were interpreted by us as connected with the contraction of the kidneys, but other possibilities can of course be considered.

On account of the great similarity in clinical course and patho-anatomic picture, we consider an identity to be established as between the cases reported here and those by Fanconi *et al.*

Summary

In two families with five and three children respectively, two of the children in each family died of renal diseases with a very similar course. They fell ill manifesting fatigue, anemia, slowly increasing polyuria, polydipsia and, gradually, isosthenuria. In the urine, a very insignificant amount of protein was noted, or none at all, and the sediment showed nothing pathologic. There was hardly any increase in the blood pressure. The nonprotein nitrogen slowly increased and the children died of uremia.

In three autopsy cases, the renal changes are practically identical, showing a symmetric and diffuse contraction with severe damage to the glomerules as well as to the tubules. The histologic picture is characterized by sheath-like, thickened basal membranes, a large number of hyalinized glomerules, a variation of atrophic and hypertrophic tubules, areas with a thyroid-like appearance, and a pronounced fibrosis together with an infiltration of round cells. The structure seems to conform, in principle, to that described by Fanconi *et al.*

In the opinion of the present authors, these cases are identical with the so-called familial juvenile nephronophthisis.

Néphronophthisie juvénile familiale.

Les auteurs rapportent les cas de deux familles comptant respectivement cinq et trois enfants et dont chacune perdit deux enfants qui moururent d'une maladie des reins dont l'évolution fut pour ainsi dire identique dans tous les cas. Ces enfants tombèrent malades et présentèrent de la lassitude, de l'anémie, de la polyurie progressivement plus sévère, de la polydipsie et peu à peu de l'isosthénurie. La concentration des protéines dans les urines était insignifiante ou nulle et le sédiment ne présentait rien de pathologique. On ne notait aucune augmentation de la pression sanguine. Le taux de l'azote résiduel augmenta peu à peu et les enfants moururent d'urémie. Dans trois

cas, les altérations rénales relevées à l'autopsie étaient pratiquement identiques, les reins présentant une contraction diffuse symétrique avec altérations sévères des glomérules et des tubes urinaires. Le tableau histologique était caractérisé par la présence d'une membrane épaissie faisant office d'enveloppe avec hyalinisation de nombreux glomérules, des tubuli tantôt atrophiés et tantôt hypertrophiés, des taches d'apparence thyroïdienne et fibrose sévère avec infiltration de sphérocytes. Cette structure ressemble dans ses grandes lignes à celle qui a été décrite par Fanconi et ses collaborateurs. D'après les auteurs, ces cas sont identiques à ce que l'on appelle la néphronophthisie juvénile familiale.

Die familiäre juvenile Nephronophthise.

In zwei Familien mit beziehungsweise 5 und 3 Kindern starben je zwei Kinder in jeder Familie mit den Anzeichen einer Nierenerkrankung von sehr ähnlichem Verlauf. Sie erkrankten mit Symptomen von Abgeschlagenheit, Anämie, langsam zunehmender Polyurie, Polydipsie und nach und nach Isosthenurie. Im Harn wurde ein ganz unbedeutender oder gar kein Eiweissgehalt festgestellt und das Sediment wies nichts pathologisches auf. Der Blutdruck war kaum gesteigert. Der Reststickstoff nahm langsam zu und die Kinder starben an Urämie. Bei drei autoptisch untersuchten Fällen waren die Nierenveränderungen praktisch identisch, eine symmetrische diffuse Schrumpfung mit schweren Schädigungen der Glomeruli und Tubuli. Das histologische Bild war durch scheidenförmige verdickte Basalmembranen, eine grosse Zahl hyalinisierter Glomeruli, eine Abwechslung atrophischer und hypertrophischer Tubuli, Zonen von schilddrüsenähnlichem Aussehen und eine ausgesprochene Fibrose mit Rundzelleninfiltration gekennzeichnet. Die Struktur scheint grundsätzlich mit der von Fanconi u. Mitarb. beschriebenen übereinzustimmen. Der Meinung der Verfasser nach sind diese Fälle mit der sogenannten familiären juvenilen Nephronophthise identisch.

Nefronotisis juvenil familiar.

En dos familias con respectivamente cinco y tres hijos, mueren dos de los hijos de cada familia, de enfermedades renales que presentan cursos muy semejantes. Caen enfermos manifestando fatiga, anemia, poliuria que aumenta lentamente, polidipsia y, gradualmente, isostenuria. En la orina se presenta una cantidad bastante insignificante de proteína, o nula, y ninguna señal patológica, en el sedimento. Aumento apenas perceptible de la presión sanguínea. El nitrógeno, no proteico, aumenta poco a poco y los niños mueren de uremia. En tres de las autopsias, son casi idénticos los cambios renales, presentando una contracción simétrica y difusa, con lesiones graves de los glomérulos y de los túbulos. El síndrome histológico se caracteriza por membranas basales espesadas y envainadas, un gran número de glomérulos hialinados, una variedad de túbulos atróficos e hipertróficos, áreas con apariencias de tireoides, y fibrosis pronunciada junto con una infiltración de células redondas. La estructura parece ser conforme en principio con la descrita por Fanconi y col. Los presentes autores opinan que estos casos son idénticos a los de la pretendida nefronotisis juvenil familiar.

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Use of Analysis in Mechanics of Breathing in Provocation Test in Bronchial Asthma[1]

Preliminary Report

by INGA ENGSTRÖM, PETTER KARLBERG, GÜNTER KOCH and SVEN KRAEPELIEN

In the allergological study of bronchial asthma it is of great importance to be able to distinguish between manifest and latent allergies (7, 9). A positive skin reaction alone does not assist in this respect since it may be a sign either of a manifest or of a latent allergy. The case history is of value, but does not always constitute sufficient proof. Consequently, in order to decide whether a manifest allergy is present, the case history and skin test must be supplemented by so-called provocation tests (2, 3, 4, 8). These tests usually consist of the inhalation of allergen solutions so that the mucous membrane of the respiratory tract enters into contact with the suspected allergen. If clinical symptoms of asthma arise, the provocation test is judged to be positive.

The pulmonary changes that may be caused by a provocation test are the same as occur in an attack of spontaneous asthma, namely spasm in the smooth muscles around the bronchioli, swelling of the mucous membrane, and increased secretion, all of which hinder the passage of the respiratory air through the finer bronchi and so provide the clinical symptoms. When the changes are pronounced, the symptoms are so distinct that no diagnostic difficulties need arise. All degrees of changes are conceivable, however, and they may be so small as to be impossible to diagnose by routine clinical examinations.

As a better means of evaluating provocation tests, use has earlier been made of different kinds of respiratory test such as the determination of vital capacity and timed vital capacity (1, 5). The results have not been

[1] Aided by a grant from the Swedish Association against Tuberculosis and Other Social Diseases.

convincing, however, perhaps because of the insufficient sensitivity of the methods employed.

A direct measurement of the airway resistance before and during a provocation test should be better calculated to give indications even of small and perhaps transitory pulmonary changes. The use of such a method in provocation tests when the clinical assessment was doubtful has given encouraging results, a preliminary report of which is presented below.

Methods

The mechanics of breathing have been studied from simultaneously recorded tidal volume and related intra-esophageal pressure changes, representing the changes of the intra-pleural pressure.

A polyethylene catheter, 1 mm in diameter, is introduced through the nose so that the tip lies between the upper and the middle third of the esophagus. The catheter, which has 2–3 holes within 10 mm from the tip, is directly connected to an electromanometer (Elema). The entire system is filled with saline from an attached syringe and repeatedly flushed during the determination.

The child breathes through a mouth-piece via a 35 mm diameter tube into a $1\frac{1}{2}$ m^3 air-tight box. Pressure changes in this closed system caused by respiration are picked up by an electromanometer. After amplification the signals from the two electromanometers are recorded on a direct writing recorder (Elema's mingograph). The signals from the "volume" electromanometer are also electronically differentiated registrering air flow rate on a third channel of the recorder.

The airway resistance has been estimated from constructed respiratory loops or directly calculated according to Mead *et al.* (6).

Procedure

We have employed this method on asthmatic children with positive skin test and whose history contained a suspected allergy to some allergen, but in whom the provocation test in the normal clinical assessment was negative or doubtful. No child showed symptoms before examination or had received symptomatic therapy on the day prior to examination.

After the recording of a regular breathing curve, the patient was given the suspected allergen in aerosol form by means of a Pari-Optimal inhalator, Primus model. The time of inhalation was 5 minutes, during which about 2 ml of the allergen solution was nebulized. The breathing was thereafter recorded at 3–5 minute intervals for the following 20–30 minutes. In some cases the test was concluded by letting the patient inhale a 1% solution of Isoprenaline (Pafadrin®) for 30 seconds and recording the breathing a few minutes after the inhalation. The catheter was kept in the same position throughout the examination. The conduct of the examination usually proved simple and it caused little trouble to the children.

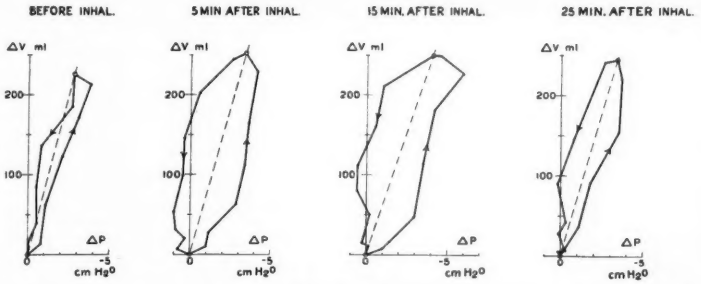

Fig. 1. Constructed respiratory loops before and during provocation test with dust allergen in a 10-year-old boy with positive skin test for dust. No clinical signs appeared.

Results

The results are shown in Figs. 1 and 2. In certain cases distinct clinical symptoms appeared during the provocation, and the airway resistance showed a marked increase. In one case with insignificant clinical symptoms a distinct, but less pronounced, increase in the airway resistance was also noticeable. This increase was recorded before the clinical symptoms became

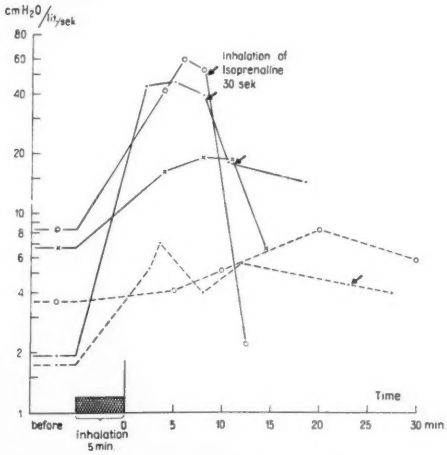

Fig. 2. Changes in airway resistance before and during provocation tests.

Case	Age (yrs)	Allergen	Clinical signs
— · —	10	"Chrysanthemum leucanthemum pollen"	Dyspnoea and rhonchi after 2 min.
— o —	10	House dust 1/100	Rhonchi after 4 min.
— x —	13	Canine epithelium 1/10	Rhonchi after 8 min.
— o —	10	Birch pollen 1/10	0 (asthma on following night)
— · —	10	Feline epithelium 1/100	0

apparent. An increase in the airway resistance was also recorded in some cases in which no clinical symptoms were observed during the provocation. Where clinical symptoms occurred, they rapidly disappeared after inhalation of Isoprenaline, and simultaneously a rapid lowering of the airway resistance was recorded.

The results showed that changes in airway resistance may be taken as an indicator of the degree of pulmonary reaction during the provocation test. Since changes in the airway resistance were demonstrable even without clinical symptoms, the method enhances the possibilities of establishing manifest allergies.

Summary

A study of the mechanics of breathing during provocation tests in cases of bronchial asthma enhances the possibilities of demonstrating manifest allergies.

Avantage de l'étude de la mécanique respiratoire, au cours du test de « provocation », chez les asthmatiques.

L'étude de la mécanique respiratoire au cours des épreuves de « provocation », chez des asthmatiques, permet de mieux préciser l'origine allergique spécifique, des phénomènes pulmonaires.

Nutzen der Analyse der Atemmechanik während des Provokationsversuchs bei Bronchialasthma.

Das Studium der Atemmechanik während eines Provokationsversuchs in Fällen von Bronchialasthma gibt grössere Möglichkeiten zum Nachweis einer manifesten Allergie.

Las ventajas del estudio de la mecánica respiratoria durante las pruebas de provocación en los asmáticos.

El estudio de la mecánica respiratoria durante las pruebas de provocación en casos de asma bronquial aumenta las posibilidades de demostración de las alergias manifiestas.

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Future Trends in Maternal and Child Health[1]

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The fiction of yesterday
is the reality of today.
The dream of today
will come true tomorrow.

International Exhibition of the Atom, Amsterdam 1957

In the history of social medicine the level of infant mortality has been the yardstick of progress in child hygiene. In some countries in Europe the total infant mortality, i.e. the mortality rate in the first 52 weeks of life per 1000 live births, has decreased under 20 and is still going down. The passing of this milestone is the motive for looking into the future of maternal and child health.

Sweden, Norway and the Netherlands have no reason for too much national pride for having reached this record although this human weakness would be understandable. Having a relatively high living standard is no merit in itself, because a complex of factors determines the situation. Still less is there reason for *medical* pride. So close is the interrelationship between the socio-economic and the socio-hygienic development, that it is no longer possible to single out the medical component as a factor in itself.

Medical modesty is the more necessary because the infant mortality rate of a whole country is an average, which means that in one and the same country there are regions or cities where the rate is higher or lower than the average. Every country has its more developed and underdeveloped areas from a socio-hygienic point of view.

The most privileged countries as far as infant mortality is concerned have regions where the rate is higher than 20, while several of the less privileged countries include regions or cities with an infant mortality of less than 20.

[1] Opening lecture of the Third Scandinavian Public Health Training Course, Göteborg, August 1st, 1957; given at the request of the Director of the Regional Office for Europe of the World Health Organization.

An infant mortality of 20 is far from a minimum, which is demonstrated by the fact that some regions, cities or groups in different countries already have an infant mortality of 15 per 1000 live births or less. This is in accordance with the historical trend. At a time that the infant mortality in Holland was between 100–150 per thousand (half a century ago) the more well-to-do families had an infant mortality of 20–30. In 1920 in Stockholm the infant mortality was 50 for the lower social classes and only 15 for the upper income groups. Even in 1954 in England and Wales figures show "that in spite of the tremendous reduction in infant mortality rates during the past 30 years, there has been no narrowing of the difference between the various social classes, i.e. no tendency for the gradient to become less steep" (1; see also 2).

The present generation of working men's families hardly enjoys the same low infant mortality as the previous generation of more privileged families. *The average of today was announced by the minimum of yesterday. The minimum of today is becoming the average of tomorrow.*

This look into the future of maternal and child health bears a Western European stamp and is therefore more or less restricted to a special region. Actually the great problems and great tragedies in maternal and child health are to be found in so-called underdeveloped, better called underprivileged, countries in the world. But the perspectives in technically more developed countries are not without importance for pre-industrial regions. The difference between the present-day constellation in Western Europe and its own past in the 19th century is no greater than the distance between maternal and child health in western and eastern countries in our time. What seems to be a difference in place, actually is a difference in time (3). Future trends in maternal and child health reflect the near future in more privileged and the more distant future in underprivileged countries.

Infant mortality and child mortality in general may no longer form a socio-hygienic problem of primary importance in economically more developed countries, but the fact remains that far too many children still die.

It is therefore necessary to cast a glance on figures of maternal mortality and of child mortality of different age groups in different countries to learn the present minimum according to social class, season and urbanisation. Minima of mortality are the promise of the immediate future.

In several European countries maternal mortality has now reached a figure of as low as 5–10 per 10,000 deliveries against 20–40 just before the Second World War, while in special groups 3 in 10,000 is no longer unusual.

Modern prenatal care has a much wider scope than the reduction of maternal mortality. Its main aim is to keep up and to promote the health of the pregnant woman and to obtain an optimal development of the foetus.

It is of academic rather than of practical value to argue whether pregnancy

is a more or less physiological condition. Pregnancy puts a stress on the body of the woman. To meet this stress the woman must be as healthy as possible before and during pregnancy, not only in the negative sense of having no detectable disease, but still more of being in or attaining a nearly optimal state of *health*.

It is not possible to reach this goal—a primary task in social obstetrics—without being conscious of the relationship between the metabolism of body functions and stress. The understanding of sub-clinical symptoms is essential in the practice of prenatal care.

There is perhaps no period in life which offers a better opportunity for practising health education in the family than pregnancy. The time in which medical care of the pregnant woman could be restricted to obstetrical procedures has gone. The quality of nutrition of the expectant mother and the other members of the family, rest and sleep, the relationship between parents and children and many other daily problems can be discussed, together with the importance of a general medical overhaul and early and repeated prenatal examinations. The significance of prenatal care in its broader sense, not only for the mother but also for the whole family and for the future of the family, cannot be overestimated. In short, social obstetrics has become an integral part of public health care for the individual, the family and the group or community. It even includes the practice of (polio)vaccination.

As a matter of fact social obstetrics demands the best natal care which can be given. It is a simplification of a complicated problem to assert that a choice must be made between domiciliary midwifery and complete hospitalisation. The situation not only varies from country to country and from region to region, according to history, tradition and medical services, but side-issues, such as care of the newborn in general and premature-care in particular, may be decisive.

The level of the perinatal mortality, i.e. stillbirth rate and mortality in the first week of life combined, is not the only yardstick for the evaluation of natal care but is an important one. However, evaluation is not possible without comparing the results and figures of different regions or countries (4). This example introduces two concepts in modern maternal and child health and in public health in general: *the role of evaluation and of comparative research*. They are so closely connected as to be inseparable.

Applied to the problem of perinatal mortality in the Scandinavian countries and in the Netherlands this method of approach gives interesting figures. Norway seems to have the lowest stillbirth rate of 13–14 per 1000 and the lowest first week mortality of less than 10. A perinatal mortality of 20–25 per thousand is no longer a theoretical aim, but has been realised.

Oslo has a perinatal mortality of less than 20. The same holds true for the large group of more than 70,000 domiciliary deliveries in Holland where maternity home help is given (5).

Until recently a perinatal mortality of 30 seemed to be a reasonable goal. Future trends point at 15 per 1000 births. Perinatal mortality is no longer the hard core of infant mortality which it seemed to be.

Perinatal mortality deserves our greatest attention. In Holland—and roughly the same holds true for the Scandinavian countries—perinatal mortality amounts to about 10% of the total mortality of all age groups together.

The number of stillbirths alone is nearly as high as that of *all* deaths from violence in *all* age groups combined. In comparison with perinatal mortality the importance of the common infectious diseases and of tuberculosis as causes of death becomes insignificant. In the first three days of life as many infants die as in the remaining 362 days of the first year (6).

In principle these conditions are more or less the same in our countries, notwithstanding great differences in medical services. The most striking resemblance is the fact that the rate of perinatal mortality is practically the same in Sweden and in Holland (Sweden being somewhat in advance), notwithstanding the divergence in obstetrical care: in Sweden nearly 100% hospitalisation, in the Netherlands only 25%. This resemblance in figures and difference in policy suggest that various methods may give the same results, which teaches us medical modesty.

Above all it shows that it is indispensable to practise comparative research to prevent us from drawing conclusions from the results of one method, while actually the same results are obtained by different ways. Scandinavian countries and the Netherlands could give an example by organising a system of comparative research on the basic facts of perinatal mortality, without going too much into details. This comparison is important not only from a scientific point of view, but above all for the practical purpose of evaluating the merits of different methods in order to select the best elements and to combine them. This kind of analysis and synthesis shows us future trends and the necessity of leaving antiquated channels.

Birth rates in Sweden, Norway and Denmark are lower than in the Netherlands. The total number of births in the three Scandinavian countries is hardly higher than in the Netherlands alone.

In tracing the comparison through the whole domain of infant mortality it is generally known that Sweden has achieved in the last 5 or 10 years nearly the lowest total infant mortality in the world, now reduced to 17 per 1000. This is still far from a minimum. In all our countries, regions and cities are known where the infant mortality rate is under 15. In 1954 Oslo

TABLE 1

Perinatal and infant mortality 1954, Scandinavia and the Netherlands.

Country	Live births No	Live births ‰	Stillbirths	First week	Perinatal mortality[1]	First month	First year[2]
Finland	89,845	21.4	18.0			19.2	30.6
Denmark	76,365	17.3	19.3	15.5	34.8	18.0	26.9
Norway	62,739	18.5	14.4	10.0	24.4	11.8	21.4
Sweden	105,096	14.6	16.9	12.0	28.9	13.9	18.7
Netherlands							
1948		25.3	18.9	13.8	32.7	17.4	28.6
1954	227,840	21.6	17.3	12.7	30.0	14.7	21.2
1956		21.2	16.9	11.1	28.0	12.9	19.0

[1] Perinatal mortality has been taken as the sum of stillbirths (per 1000 births) and first week mortality (per 1000 live births). Strictly speaking this is not correct, but it serves for practical purposes.

[2] Total infant mortality (per 1000 live births).

had already a total infant mortality of 14, while in the whole of Norway the rate was 21. Even in 1920 a rate of 15 had been reached in the higher social classes in Stockholm. The low total figure of Sweden shows interesting and instructive aspects. While the first week mortality is not extremely low, the infant mortality after the first week of life amounts to 6–7 per 1000 and after the first month to 4–5, half the rate in other Scandinavian countries.

As far as infant mortality is concerned at the moment:

Sweden is 2–3 years in advance as compared to the Netherlands and Norway,

The Netherlands and Norway are 5–6 years in advance as compared to Denmark,

Denmark is 1–2 years in advance as compared to Finland.

Again what seems to be a difference in place, actually is a difference in time. A comparison between the two halves of Fig. 1 illustrates this historical law.

Two questions arise:

(1) why is the perinatal mortality lower in Norway than in Sweden, while the reverse is the case for infant mortality after the first week?

(2) why is perinatal mortality in Sweden not lower than in the Netherlands notwithstanding the following facts:

(a) Sweden has nearly 100% hospitalisation of deliveries against 25% in the Netherlands.

(b) infant mortality after the first week is constantly lower in Sweden than in the Netherlands.

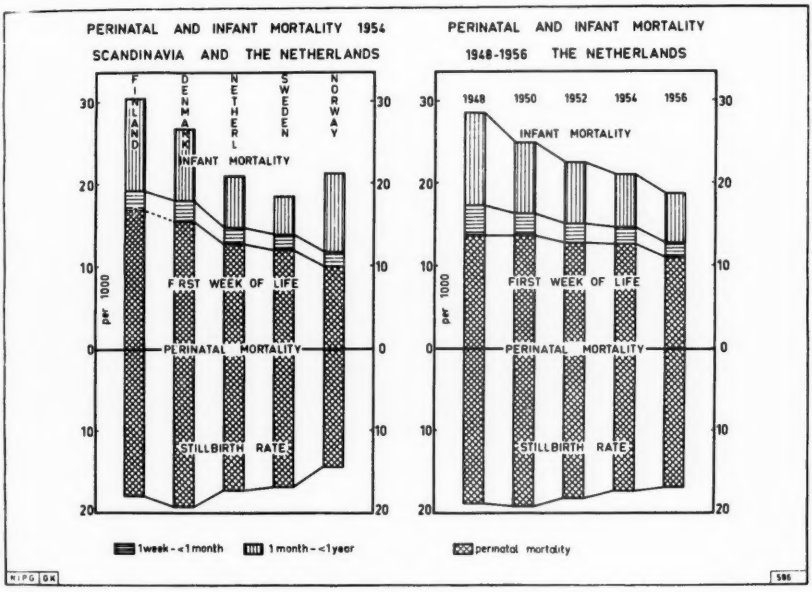

Fig. 1.

The answer to both these questions, which can only be given by comparative research of basic facts, is not only of great importance for the countries concerned but no less for the elucidation of the problem of perinatal mortality in general.

Notwithstanding these differences in infant mortality in neighbouring countries, present figures demonstrate that *infant welfare centres, which are visited for the first time when the child is 3–6 weeks old, can no longer fulfil their original task of reducing drastically a high infant mortality.* Nowadays they can only slightly reduce a relatively low infant mortality. This has become their secondary task, which should, however, not be neglected. Their primary task has become the promotion of health during the first years of life. The negative aim of reducing the mortality has been replaced by the positive task of health promotion, which has become the motto of public health work in general. There is, however, no age group where it can more easily be attained and better be demonstrated than in the first year or years of life.

By knowing the past trend of infant mortality in the most advanced countries it is possible to predict the future trend in a comparable country. Denmark had an infant mortality of nearly 27 in 1954, Sweden had the same

TABLE 2

Child mortality rates 1954, Scandinavia and the Netherlands per 10,000.

Country	Age group									
	Infants		1–4		5–9		10–14		15–19	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Finland[1]	346	261	20	13	8	5	6	5	12	6
Denmark	309	221	14	11	4	3	3	3	9	4
Norway	246	187	12	10	7	5	6	3	9	4
Sweden	224	154	11	9	5	4	5	4	9	4
The Netherlands . . .	238	191	15	12	7	4	5	3	7	4

[1] 1955.

rate in 1946 and the Netherlands in 1949. A rate of 20 was reached in Sweden in 1952 and in Holland in 1955: in both countries the road from 27 to 20 per 1000 in the development of infant mortality has been covered in six years.

Assuming that an acceleration in this development takes place it may be expected that Denmark will have reached an infant mortality of about 20 in 1958–1959, already preceded by a relatively low mortality at pre-school and school age.

It is less certain but most probable that at the same time Sweden, and in 1960 Holland, will have achieved an infant mortality of 15. In 1965 an infant mortality of 10 will be something "normal".

Mortality figures of pre-school age, school age and adolescence in the Scandinavian countries and the Netherlands show less variety than the rates of infant mortality. Sweden takes the lead up to 5 years of age, Denmark during school age and Holland during adolescence. There is a tendency of pre-school child mortality to converge to 10 per 10,000. The second year of life has a mortality rate twice as *high* as the 2–4 age group, but 10 times as *low* as the total infant mortality.

The mortality figures of *young* school children move to 3 for girls and 5 for boys. In technically advanced countries mortality in *older* school children is so low—the lowest of all age groups—that international differences tend to disappear. The curves show that the decrease slows up at a level of 4–5 per 10,000. The rate tends towards a minimum of 2 per 10,000. Will it be possible, by reducing fatal accidents and respiratory infections, to reach this minimum for child mortality in general after the first year of life? It seems over-bold to aim at this target, but "the dream of today will come true tomorrow".

In adolescence mortality figures go up again in comparison with older

TABLE 3

Difference between actual deaths and present minima in younger age groups.[1] *Sweden 1954.*

Age group	Actual deaths		Present minima		
	No (A)	per 10,000	per 10,000	No (M)	A–M[2]
Stillbirths	1811	169	100	1070	740
Infants	1966	187	140	1470	500
1–4 years	437	10	7	310	130
5–9 „	279	4	3	190	90
10–14 „	225	4	2	110	120
15–19 „	278	6	4	175	100
Total 0–19	5000				1680
20–29 years	880	10	7	640	240

[1] Deaths calculated from minima already reached in special regions or groups in some countries.
[2] Rounded figures.

school children, even if tuberculosis has become unimportant. Adolescent girls show however that a level of 4 per 10,000 can be reached in this more vulnerable age group.

During infancy there exists an almost constant excess of mortality for boys (130 to 100). This sex ratio is less pronounced during pre-school age, but increases again in school age and adolescence. The decrease of tuberculosis mortality has influenced this ratio, the girls profiting relatively more than boys.

Nearly twice as many adolescent boys as girls die today. Accidents, of which boys are more often the victim, are the principal cause of this difference.

In the past half century a spectacular decrease of child mortality in all age groups has occurred in technically more advanced countries. During the next half century the decrease will continue, though seemingly less spectacular. Vital statistics point out future trends, which can be accelerated or retarded by a more or less well planned socio-economic and socio-hygienic development.

In comparing the actual number of deaths with the minima found in special regions or groups—even in a country with such low mortality rates as Sweden—1500–2000 lives could be saved annually on a total of 5000 (6000) deaths from 0–20 (30) years.

It is only realistic to predict that within the next decade in every country thousands of child lives will be saved annually, notwithstanding the already

relatively favourable figures at present. Medical thinking has to keep pace with this rapid evolution and its repercussions.

The main lesson to be learned from this development is the sober fact that death rates in themselves cannot now be regarded as an indication of socio-hygienic conditions during childhood, as they were in the past century and up to about 1920. However important they are, they do not indicate the level of *health* in children.

The wide gulf between death on the one hand and optimal health on the other is not sufficiently appreciated. Child mortality has become a concept of the past and optimal health is the aim of the future. Low death rates give the misleading impression that social medicine is reaching its ultimate goal; such is far from being the case (6).

All efforts can now be directed towards improvement of health and thus towards the promotion of happiness for children. In childhood, death, and to a certain extent illness as well, are becoming almost legendary. Nevertheless, low death rates should not lead to complacency but rather should stimulate the efforts towards the optimal development of the child in terms of full health.

Knowledge of *child development*—a concept which is insufficiently defined by the term growth—forms the base of modern child hygiene. In the study of child development physical and mental growth are considered to be one inseparable entity.

The observation of growth and development of the individual child in its longitudinal trend from conception until adulthood is the ABC of modern child health. Notwithstanding the complicated character of the growth process, it is possible to construct a growth diagram of the so-called average child, who in fact does not exist. If the salient aspects in the individual development of the child from 0–20 years are included in the growth chart, an overall picture is formed which is indispensable for estimating the state of health of the child in its broader sense. These salient aspects are among others height and weight, chemical growth, dentition, hemoglobin, motoric and mental development, social behaviour, emotional conduct, sexual development, and so on.

Child health in its modern concept is based on the study of child development, be it of the individual child or of certain groups of children. This approach presupposes that the doctor becomes more "health-minded" than "disease-minded". Until now the contrary has usually held true.

The future demands doctors who are primarily human biologists instead of clinicians. Maternal and child health practised as preventive medicine still emphasises the negative aspect, maternal and child health practised as child biology emphasises the positive side of health control and health promotion.

It is not possible to pursue the development of a child or of a group of children by obtaining a momentary impression during so-called routine examinations. These examinations may be of importance for detecting malformations or other disturbances, but they are so rarely done and they were so much directed towards giving a transversal section of the state of health through clinical eyes that they can only give a static idea of the situation at a special moment, but not a picture of the development of the child, which is a dynamic process.

To serve this purpose every period of childhood—as an infant, pre-school child, school child and adolescent—must be followed carefully, in accordance with the special aspects of the biological development in each period.

At the end of the observations in each age group the different periods are brought together to build up a "film" of the development of the child. Few subjects in medicine are so fascinating as child development.

Together with the decrease of mortality and morbidity, secular trends going on slowly but persistently have influenced child development more strongly than has been anticipated. This tendency is illustrated by the fact that in our countries military recruits had a height of 170 cm in 1920 against 175 cm in 1950. It can be put in another way: in the last 20 years the development of the child has been advanced by one year. The average child of 10 years of today has reached the same state of development as the average child of 11 years 20 years ago. This secular process is still going on. It means that factors like malnutrition, repeated illness and mental frustration which retarded growth in the past gradually lose their ominous influence, but the differences in growth according to social class still exist.

During the growth process from 0–20 years a superposition of the secular trend on top of the individual development takes place.

Research in child development is not only of great importance for medicine in general and for social pediatrics in particular, but is also of great practical significance in everyday life.

Clothes and shoes of the child have to be adapted to the present development. This view is penetrating to industry. Also in the construction of school furniture it is being taken into account. It has been adopted to a certain extent in the manufacture of toys.

The study of child development begins with the newborn child, if not with the fetus. Until recently the newborn child was more or less neglected in maternal and child health. Obstetric-pediatric teamwork is developing more and more, be it not yet everywhere in an ideal way. Biologically speaking maternal health and child health are inseparably connected.

The increasing relative significance of first day and first week mortality

demands systematic and experienced observation and care of the newborn in general—from birth onwards—and of the premature and weak child in particular.

Infant care during and after the newborn period has more and more an educational character, without however neglecting prevention and treatment of minor or major diseases. Raising the level of maternal care is the best way of coming to an optimal development of the infant.

This approach demands an individual contact with the mother—the classical and at the same time highly modern basis of medical work. For the doctor in charge of the welfare centre it is more important to have insight into the biological development of the infant and the psychology of the mother than to have experience in rare diseases, although elementary clinical knowledge is indispensable in giving an adequate medical care.

It is more and more accepted that pre-school age is the most vulnerable period in human development. Therefore the care of the pre-school child must even more be based on the concept of child development than the care of the infant. Care of the pre-school child demands an approach of the child in the light of the biological development from 1–6 years, against the background of family, community and society.

Ophthalmological, audiological and logopedic examinations are more and more practised amongst toddlers, not to speak of the necessity of dental care. Medical examination, in the technical sense of the word, although indispensable, no longer has the last word.

The right approach is of special importance. This hardly needs mentioning in Scandinavian countries, where the equipment of day-nurseries and nursery-schools expresses a modern spirit and where a proper nutrition is taken for granted.

The methodology of medical care of pre-school children has seldom been based on the principle of child development. In general the *evaluation* of methods is weakly developed in the organization of child health, as in public health in general. This is reflected in the care of the infant, pre-school and school child. The routine examination of the school child seems for a large part still to be based on the practice of a period, when the prevention of diseases and malnutrition was more important than the active promotion of health. A break-through in the methodology of school medicine in order to develop it into school *health* is a requirement of modern child hygiene.

The millions of school children form a tremendous medico-biological bulwark. As an organised group they are accessible to well planned individual and social care, which may be decisive for their future status.

The older the child becomes, the more maternal care is supplemented by

external influences. The school plays an important part in this, without knowing, or at least satisfying, the requirements of the child during the (imperceptibly merging) phases of development.

The so-called age of the child sees more crowded and old-fashioned school classes than modern school environments. As a rule the curriculum does not quite follow the elementary insight into the mental development of the child.

The care for mentally deficient children is gradually being developed, but their counterparts, the mentally gifted, remain without special care, although their development may be anything but harmonious.

Society permits itself the luxury of entering the atomic age without paying special attention to the gifted. It is impossible to continue this neglect of the greatest treasure of a people, its gifted youth, with impunity. This neglect avenges itself already in pre-school children, but especially at the age of adolescence, unfavourably influencing the whole development of the individual gifted child.

Little attention has been paid as yet by public health to the last phase of childhood, adolescence. After elementary school the child enters the factory, office or secondary school with insufficient protection. In technical schools school health and industrial hygiene converge. They supplement each other to a greater extent than was realised up until recently.

The arrears in adolescent care can be converted to a lead, if medical care in puberty and adolescence is built up on the basis of child development and not on old-fashioned routine.

Adolescent care should become an important branch of the new child health, integrated into the organization of public health.

The requirements at the basis of a new child health are determined in the light of socio-biological insight. *The continuity which characterises the development of the child, should be the basis for the organization of child health.* Prenatal, infant, pre-school child, school child and adolescent care should merge imperceptibly and be coordinated. For girls adolescent and prenatal care partly overlap (Fig. 2).

The growth diagram of the development from 0–20 years is also the basis for the appreciation of the health of the young adult. The new child health administration is conscious of the fading away of boundaries between health care for children and adults.

It is not at all inconceivable for the child health worker that the history of social and clinical pediatrics may furnish many lessons for care of the aged. "Les deux extrêmes de la vie se touchent." Nutrition and sleep show parallels and the need for care returns at life's eve.

Before older adults have need of this care, they leave, as grandparents, a stamp upon the bringing up of their grandchildren. It is suitable in the

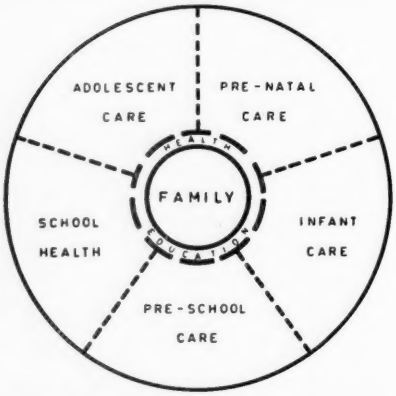

Fig. 2. Continuity in MCH-organization.

constellation of the new child health programme to find grandmother and grandfather courses next to mother and father courses.

As a rule the mother is the central figure in the family and therefore, in child care, this is expressed in the phrase maternal care.

Just as it is impossible to separate health care from socio-economic conditions, it is equally impossible to divide child health from health care as a whole. Partly unobserved, child health has entered into general health care and has been assimilated. This also holds true for the fight against tuberculosis, infectious diseases, and other ramifications of public health, and up to a certain point for curative medicine as well.

On the one hand the ties between clinical and social pediatrics have been weakened through sickness and death becoming more rare. On the other hand, however, they have been strengthened by reason of the new territories which have been explored, re-education of invalid children being an example. It is in a similar borderline territory that the care for asthmatic, diabetic and epileptic children operates. Antibiotics play a no less important role in chinical as in social medicine and pediatrics.

In the detection of children with congenital heart malformations clinical medicine has given an impulse to social pediatrics.

During the post-war decade in technically developed countries the tuberculosis figures have cascaded down. Infectious diseases have become more or less negligible. Venereal diseases have almost disappeared. Mortality figures have gone down more and more and have achieved an unforeseen record.

It would appear that a more intensified mass inoculation is in the process of banishing diphtheria and alleviating the serious effects of whooping cough. For poliomyelitis this is taking place in an unexpectedly quick way.

Typhoid (actually without inoculation) has been the forerunner in this process of extinction of the classical infectious diseases. Other salmonelloses, although less serious, are however replacing it more and more.

Nutrition of the population in general has improved, the greatest advance in social medicine in the last decades. The public—and the doctors up to a certain point—have become nutrition- and vaccination-minded.

These developments do not alter the fact that we are still a long way from having attained the Utopia of social medicine. The housing shortage, the overpopulation of our schools, the lack of teachers, the problems posed by the aged, and poverty which has not yet disappeared, are some of the stains upon our modern civilisation. However, they exist and there is little chance of them disappearing soon.

As the importance of tuberculosis and infectious diseases diminishes as a cause of death, that of tumours increases relatively. This has led to tumours and leukaemias together taking second place as causes of death during childhood. Are we on the eve of the preliminary attack on malignant disease?

The happy fluctuation in the pattern of diseases—in connection with the rapid fall in child mortality—has a special significance for clinical and social pediatrics. The syndromes for which children are hospitalised are rapidly changing. Common child diseases are being replaced more and more by rare ones. This again places a stress upon children's hospitals. We are witnessing a revolution which is raising diseases and causes of death from places low on the list to ones at the head.

Accidents furnish the most startling and tragic proof. They have become the prime cause of death for the age group from one to thirty while only occupying the third or fourth place about 1920. The organization of child health has in a recent past not paid sufficient attention to this shift.

Non-fatal (serious) accidents, which are several times more numerous than fatal ones, deserve no less urgent attention. Invalidism for a child has its consequences during his whole life. Prevention of accidents and invalidism is a task to which public health and child health should apply itself wholeheartedly.

On the one hand technical hygiene gets a new look; on the other hand classical measures keep their dominant value.

Iodine prophylaxis in regions which favour the development of goitre is still of inestimable value. Fluoridation of drinking water or milk is destined to reduce dental caries radically from infancy onwards, one of the most widespread ills in the world.

Another example of food fortification is the vitaminisation of margarine, which has raised the provision of vitamin A and D in a simple but effective

way. Vitaminisation of milk has the same effect of dealing the last blows to rickets and of bringing vitamin A consumption up to a reasonable level.

Environmental sanitation strongly influences public health and maternal and child health, much more than direct medical measures can do.

Whatever the character of socio-medical activities, a clear explication to the public is of predominant importance.

Public health, and still more maternal and child health, are loosing their statutory task more and more. *Health has become a part of life*, to be integrated into all forms of general and child education, instead of being forced by not understood control measures. A recent and impresssive example of public health as a part of life is the willingness and even pressure of public opinion to get polio-vaccination. This modern outlook of the public and doctors compels us to meet as quickly as possible the health needs of the people for whose benefit we work.

In non-verbal education at schools by way of school meals, modern school furniture and especially by modern equipping of day nurseries and nursery-schools, Scandinavian countries have given a fine example.

Child health has become a part of general health care and can only be practised fruitfully within this framework. This integration is not at variance with the development of medical history, but is in agreement if we attempt to look at the historical process in its wider sense. In this connection it is hardly of importance whether this development has been more or less planned. Probably the influence of planning on historical events is generally less than human presumptuousness would have us believe. This does not lessen our duty and desire to give our views on the near future, in which we see research and practical child health as a unity, as closely linked as light and shadow, and in which so-called theoretical and applied research are fused, together with the evaluation of method and the critical analysis of results. In future the part played by field research will become increasingly important.

New tendencies in public health and maternal and child health ask for a new orientation in training of personnel, a basic task for meeting present and future needs. Undergraduate teaching in social medicine is being introduced in recent years in our universities, but teaching of social pediatrics in its modern sense hardly takes place. To make good these arrears refresher and postgraduate courses are indispensable, not to speak of the necessity of training specialists in public health and maternal and child health.

Postgraduate and special training courses are no less necessary for nurses as for doctors. The public health nurse, whether district nurse, health visitor or school nurse, remains the backbone of public health and maternal and child health care. Other members of the maternal and child health team need a modern training as well.

The district is the open air laboratory of the public health worker. Research and administration are closely connected in public health and in maternal and child health. Together they lead to a flexible organizational policy, in the realisation that data and conditions change rapidly in this quickly changing world. The human mind lags behind technical progress.

The new orientation of child health adapts itself to modern conditions in a civilisation entering the atomic age. Research, evaluation of methods and organization deserve, in their interdependence and their interrelationship, to be adjusted towards this modern constellation which they have not yet sufficiently attained.

The new orientation of child health demands from its servants a medico-biological attitude, tending more towards health than sickness, an attitude with socio-biological vision and an imagination which does not lag behind the tempestuous developments which society is going through.

Summary

An orientation of modern child care viewed in the light of the trend in Scandinavia and the Netherlands places the following concepts before us.

Now that infant mortality has reached a level of twenty per thousand births, we have arrived at an important point in the development of child care. This fact forces us not only to form an impression of the past and present, but likewise to look to the near future. A relatively drastic reduction of child mortality is still possible, although it is less spectacular than in the past. The rates in the near future can be predicted. Now that serious illness and death in children have become a secondary problem—except for perinatal mortality, some acute diseases, some chronic illnesses and the problem of accidents—the essential task of child health care has become the active promotion of the health of the child in order to achieve an optimal development.

The doctor, if he wishes to acquit himself properly of this task, should have some idea of socio-biology and vital statistics, a knowledge of child development and experience in public health, of which maternal and child health is a part that is closely connected to other branches. More and more maternal and child health is integrated into public health. Continuity and coordination in maternal and child health should be assured from conception up to and including adolescence. The observation of growth and development of the individual child in its longitudinal trend from birth until adulthood is the ABC of modern child health.

The new child health strives towards an optimal development of the child and thereby towards optimal conditions in family, school and society. The term "maternal and child health" expresses more clearly than "child hygiene" what social obstetrics and pediatrics attempt to achieve. The continuity which characterises the development of the child should be the basis for the organization of maternal and child health.

The new orientation of child health adapts itself to modern conditions in a civilisation entering the atomic age. In their interdependence and their interrelationship research, evaluation of methods and organisation deserve to be adjusted towards this modern constellation which they have not yet sufficiently attained.

Résumé

Une vue d'ensemble de l'hygiène infantile moderne dans le cadre de son développement en Scandinavie et aux Pays-Bas, nous place devant les points suivants. La mortalité infantile ayant atteint le niveau de vingt par mille naissances, nous sommes arrivés à un stade important de l'hygiène infantile. Cet état de choses nous oblige non seulement à nous former une idée du passé, mais également à jeter un coup d'œil sur l'avenir. Les taux du proche avenir peuvent être predits. Une diminution relativement drastique de la mortalité de l'enfant est encore possible, bien que de façon moins spectaculaire que par le passé et le présent. Les maladies graves et la mort des enfants étant devenues des problèmes d'ordre secondaire — exception faite de la mortalité périnatale, de quelques maladies aiguës ou chroniques et du problème des accidents — la tâche essentielle de l'hygiène infantile est devenue de promouvoir activement la santé de l'enfant, afin d'obtenir un développement optimal. Si le médecin veut s'acquitter convenablement de cette tâche, il lui faudra avoir quelques notions socio-biologiques et bio-statistiques (« vital statistics »), une connaissance approfondie du développement de l'enfant (« child development ») et une certaine expérience de la santé publique, dont la protection maternelle et l'hygiène infantile forment une part étroitement liée à d'autres branches. La protection maternelle et infantile est de plus en plus intégrée à la santé publique. En protection maternelle et infantile la continuité et la coordination devraient être assurées dès la conception jusqu'à l'adolescence, celle-ci inclue. Observer la croissance et le développement de l'enfant individuel dans son cours longitudinal de sa naissance jusqu'à son état adulte, voilà l'ABC d'une hygiène infantile moderne. La nouvelle hygiène infantile vise à un développement optimal de l'enfant, allant de paire avec des conditions optimales dans la famille, à l'école et dans la société. Le terme « protection de la santé maternelle et infantile » exprime plus exactement que celui de « hygiène infantile » ce que l'obstétrique et la pédiatrie sociales essaient d'atteindre. La continuité, qui caractérise le développement de l'enfant, devrait servir de base à l'organisation de la protection maternelle et infantile. L'orientation nouvelle de l'hygiène infantile s'adapte aux conditions modernes d'une civilisation au seuil de l'âge atomique. Les recherches scientifiques, l'évaluation des méthodes et l'organisation méritent d'être ajustées — dans leur interdépendance et leur étroite liaison — à cette constellation moderne, qu'elles n'ont pas encore suffisamment atteinte.

Zukünftige Richtungen in Mutter und Kindergesundheitspflege.

Die Orientierung der modernen Kindergesundheitspflege betrachtet im Lichte der in den skandinavischen Ländern und den Niederlanden eingeschlagenen Richtungen gibt uns folgende Ideen ein. Mit Kindersterblichkeit auf einem Niveau von nur 20 per Tausend sind wir zu einem bedeutsamen Punkt in der Entwicklung der Kinderwohlfahrt angelangt. Diese Tatsache zwingt uns, nicht nur von der Vergangenheit beeindrucken zu lassen, sondern auch unseren Blick auf die nahe Zukunft zu lenken. Eine verhältnismässig drastische Reduktion der Kindermortalität ist noch möglich, wenn auch weniger dramatisch als in der Vergangenheit. Gegenwärtig, wo schwere Erkrankungen und Todesfälle unter Kindern ein zweitrangiges Problem darstellen — mit Ausnahme der perinatalen Sterblichkeit, gewisser akuten und chronischen Krankheiten und der Unfälle, — ist eine aktive Förderung der Gesundheit des Kindes mit dem Ziel, optimale Entwicklung zu erlangen, zur wesentlichen Aufgabe der Kindergesundheitspflege geworden. Der Arzt, der seine Pflicht gehörig zu erfüllen wünscht, muss

einen Begriff von Sozialbiologie und Lebensstatistik haben, eine Kenntnis von der Entwicklung des Kindes und Erfahrung in öffentlicher Gesundheitspflege, in welcher die Mutter und Kindergesundheitspflege einen mit anderen Zweigen eng verbundenen Teil bilden. Immer mehr wird die Mutter und Kinderfürsorge zu einem integralen Bestandteil der öffentlichen Gesundheitspflege. Kontinuität und Koordinierung in Mutter und Kinderwohlfahrtsdienst muss vom Moment der Befruchtung bis zum und einschliesslich das Jugendalter sichergestellt sein. Die Beobachtung des Wachstums und der Entwicklung des individuellen Kindes in ihrer longitudinalen Richtung von der Geburt bis zum Erwachsenenalter bildet das Abc der modernen Kindergesundheitspflege. Die neue Kindergesundheitspflege strebt die bestmögliche Entwicklung des Kindes und mithin die optimalen Bedingungen im Leben der Familie, der Schule und der Gesellschaft an. Der Begriff Mutter und Kindergesundheitspflege drückt klarer als der Begriff Hygiene des Kindesalters aus, was soziale Geburtshilfe und Pädiatrie zu erlangen bestrebt sind. Die Kontinuität, welche die Entwicklung des Kindes kennzeichnet, muss die Grundlage für die Organisierung der Mutter und Kindergesundheitspflege bilden. Die neue Orientierung der Kindergesundheitspflege passt sich den modernen Bedingungen einer in das Atomenzeitalter eintretenden Zivilisation an. Forschung, Auswertung der Methoden und Organisation verdienen in ihren gegenseitigen Abhängigkeit und Beziehungen eine Anpassung an diese moderne Konstellation die sie noch nicht genügend erreicht haben.

Orientación futura de la salud materna e infantil.

En la orientación de la puericultura moderna — considerada bajo el aspecto de las tendencias existentes en Escandinavia y Holanda — se advierten los conceptos siguientes: Como la mortalidad infantil ha alcanzado el nivel de un veinte por mil nacimientos, se ha llegado a un punto importante en la evolución de la puericultura. Este hecho nos coloca ante la obligación de formarnos una impresión acerca del pasado y de echar una mirada en el próximo futuro. Una reducción relativamente radical de la mortalidad infantil es cosa aún asequible, si bien ya no en forma tan espectacular como la ofrecida en el pasado. Actualmente, cuando las enfermedades graves y muerte infantiles, constituyen problemas de orden secundario — salvo excepciones de mortalidad prenatal, de ciertas enfermedades agudas y otras crónicas, junto al problema de los accidentes — en puericultura, la tarea esencial está constituída por la estimulación activa de la salud del niño, con el fin de realizar un óptimo desarrollo. El médico, si desea cumplir debidamente con su cometido, deberá tener alguna idea de las cuestiones sociobiológicas y de estadística vital, un conocimiento del desarrollo infantil y experiencia con respecto a la salubridad, de la que la materna e infantil, forman parte en estrecha relación con sus otras dependencias. Va integrándose siempre más la salud materna e infantil en la pública. Debieran estar aseguradas la continuidad y coordinación de la salud materna e infantil desde el momento de la consepción hasta la adolescencia inclusivamente. La observación del crecimiento y desarrollo del niño individual en su curso longitudinal a partir del nacimiento hasta la edad adulta, constituye el ABC de la puericultura moderna. La nueva salubridad infantil estriba en conseguir un óptimo desarrollo de la criatura y correspondientes condiciones óptimas en la familia, escuela y sociedad. Los términos de salud materna e infantil expresan más claramente que la palabra higiene infantil lo que la obstetricia y pediatria sociales se esfuerzan en realizar. La continuidad que caracteriza el desarrollo infantil, debiera constituir la base de la organización objeto de la salud materna e infantil. La nueva

orientación de la puericultura se adapta a las condiciones modernas de una civilización que entra en la era atómica. La investigación, la evaluación de métodos y organizaciones, merecen, en su interdependencia e interrelación respectivas, ajustarse a esta constelación moderna, a las exigencias de la cual no satisfacen aún en forma suficiente.

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Meeting, October 20, 1957

B. Rydenstam: **ECHO-virus infections.**

In Sweden ECHO-virus types 4, 6 and 9 have been isolated in cases of aseptic meningitis. During the summer and fall of 1957 epidemics of ECHO-9 occurred throughout almost the entire country. In the Uddevalla region the epidemic culminated during July and August. The majority of patients was taken care of at home, but 84 were treated at the Central Hospital. The age distribution was the following: 0–4 years, 28 cases; 5–9 years, 20 cases; 10–14 years, 16 cases; over 15 years, 20 cases. Virological examination was carried out in 18 cases, and in 11 ECHO-virus type 9 was isolated.

The ECHO-9 disease may occur as an acute infection without characteristic symptoms. To a large extent, however, it runs with meningoencephalitis, and frequently the patients exhibit an exanthema similar to that of rubella. The clinical picture varies somewhat in the different age groups. In the youngest group the picture was often milder with fever of shorter duration, absence of clinical symptoms of meningitis and a lower cell count in the spinal fluid. On the other hand, diarrhea occurred strikingly often in this group, e.g., in 4 out of 6 children under 6 months old. Among the older children and adults this occurred only in exceptional cases. Exanthema was observed in children under 2 years old in almost all cases and thereafter in decreasing frequency with an incidence of about 1 in 4 of the cases in individuals of 15 years or over. As a rule the exanthema was also more extensive and intense the younger the patient.

Lumbar puncture was performed in 76 cases. The first puncture showed a pathologic cell count ($\geqslant 5/mm^3$) in 60 cases. In 5 of the 16 primarily negative cases the puncture was repeated and in all of these the result was positive. The total cell count was strikingly high. Whereas, for example, in cases of polio and mumps meningitis 2 and 5% respectively reach values over 500 cells/mm^3, 36% of our ECHO-meningitis cases exceeded this count. In 20% of the cases the cells were over 1000/mm^3. Pathologic spinal fluid was found in about 50% of the cases on lumbar puncture on the second day of the disease, and as a rule the meningitis appeared by the fourth day at the latest. The average number of cells in the fluid increased during the whole first week of the disease.

In Sweden Gabinus (*Svenska Läkartidn., 44:* 837, 1947) has described a limited epidemic with meningoencephalitis and rubella-like exanthema. However, in none of his cases did the cell count exceed 300/mm^3 and exanthema did not occur in infants.

Ivar Westerberg: **Urethritis in girls.**

Eleven girls, aged from 3 to 8 years, exhibited prolonged and recurrent urethral symptoms: several had enuresis during the day as well as at night, others frequent micturition with normal urine, some had recurrent cystitis and pyelitis and one had a

discharge after a traumatic injury. Routine examinations had given almost exclusively negative results. In some cases there were a few cells in the urine, and cultures showed growth of coliform and other Gram-negative rods. Urographic examination was performed in all except one case (the girl with the traumatic injury) and showed normal conditions. Urethroscopy revealed in all cases inflammatory changes in the mucous membrane, most pronounced in the posterior parts of the urethra immediately below the neck of the bladder.

Inflammatory changes may thus be of great significance as the cause of different urologic symptoms in girls. Several authors have earlier demonstrated this. In 1935 Campbell (Clinical Pediatric Urology, V. B. Saunders Comp., Philadelphia, 1951) carried out an endoscopic examination of 219 girls with persistent enuresis and found urethritic changes in 35%. Spence & Moore (*Texas State J. Med., 35:* 39, 1939) ascertained urethritis in 76% of 50 girls who had had acute pyelitis, frequent micturition in spite of normal urine and where previously no explanation of the symptoms had been found. Hodges (*J.A.M.A., 149:* 753, 1952) examined 25 girls, varying in age from 2 to 9 years, with urologic symptoms resistant to chemotherapy and antibiotics and found inflammatory changes in the urethra in the majority of cases.

In our cases the endoscopic examination gave the diagnosis. This should certainly be used more extensively than hitherto. Cases with enuresis, where the symptoms appeared after complete bladder control, where the discomforts have been especially pronounced during the day and where prolonged medical treatment and strict adherence to the prescribed regimen has not given any result, should be subjected to such an examination. The treatment has consisted of electrocoagulation of the mucous membrane combined with a prolonged vitamin A and sulfa therapy. The risk of stricture and cicatrization has made extreme caution imperative, and in many cases the electrocoagulation had to be carried out in two sessions. A definite improvement has been obtained in practically all cases, but it is still too early to give a final evaluation.

Per Selander, Malmö, Sweden

The Danish Pediatric Society

Meeting, October 2, 1957

P. Plum: **The prognosis in cerebral paralysis.**

To be published in *Annales Pædiatria Fenniae*, Vol. 3, Fasc. 4, 1957, and *Danish Medical Bulletin*.

C. Dueholm and K. Aagaard: **A case of aplastic anaemia following treatment with chloromycetin.**

A girl aged 3 years and 9 months was admitted on Sept. 5th, 1957, to the Department of Paediatrics at the University Hospital, on account of aplastic anaemia. During four weeks in June 1957 she had received a total of 22.5 g chloramphenicol in the form of chloromycetin palmitate mixture for the treatment of whooping cough. From July 9th to August 1st she was jaundiced, the feces were acholic and the liver was enlarged. On the 28th of August ecchymoses were observed on the legs and some days later pe-

techiae. On the 3rd of September anaemia, granulocytopenia and thrombocytopenia were revealed. Supplementary investigations after admission confirmed the diagnosis of aplastic anaemia. On a basis of cases described previously, it appears probable that the extreme reduction of bone-marrow function was a sequel of treatment with chloramphenicol. The prognosis and treatment were mentioned. Finally, it was emphasized that treatment with chloramphenicol always involves the risk of the development of aplastic anaemia.

(To be published in *Ugeskrift for Læger.*)

Discussion.—*J. Kringelbach* reported a case history of a girl aged 7 years, who previously had suffered repeatedly from catarrhal conditions with occasional episodes of otitis and sinusitis. Adenotomy gave no improvement. During the first year of life she was treated several times with penicillin until she developed urticaria following an injection of penicillin. In April 1957 she developed whooping cough and was treated with chloromycetin palmitate, a total of 11 60 ml bottles = 660 ml = 20,625 mg or approximately 825 mg per kg body weight being administered. The period of treatment extended intermittently from April 6th, 1957, to June 27th, 1957. From the middle of June 1957 she had been strikingly pale and tired and gradually a tendency to haemorrhage in the skin was observed. In the middle of July 1957 the child had diarrhea for a week. On August 1st, 1957, she developed tonsillitis and was treated with penicillin orally. On August 8th she was admitted to the Department of Paediatrics, the Central Hospital, Nyköbing, Falster. Investigation revealed agranulocytosis, thrombopenia. Probably aplasia of the bone-marrow, affecting granulopoesis, thrombopoesis and erythropoesis. The child was treated intensively for 6 weeks with blood transfusions, Meticorten, ascorbic acid, vitamin B_{12} and iron, but frequent epistaxes still occur and there is pronounced anaemia and thrombopenia. Attention was drawn to the connection between the occurrence of toxically conditioned aplastic anaemia and allergic disposition which has been confirmed in reviews from abroad. The employment of chloromycetin in allergic children was warned against. There is no indication whatsoever for the employment of this preparation in the treatment of whooping cough in children over the age of 6 months to 1 year. In infants the preparation may be administered on vital indications, but why should not one of the less dangerous tetracycline preparations such as terramycin be employed instead? — *J. Flamand Christensen* stressed the serious nature of the problem by reporting that he had undertaken an investigation of a series of children under the age of 1 year and this revealed that 60 per cent of the infants had received antibiotics prior to the age of 1 year. — *E. Thamdrup* inquired about the incidence of aplastic anaemia following administration of terramycin and aureomycin. — *J. Kringelbach:* Agranulocytosis has also been seen following administration of penicillin and terramycin. The risk is given as not more than 1:10,000 and not less than 1:100,000. In general the administration of these antibiotic preparations must be warned against in children with allergic reactions. The use of chloromycetin must, in fact, be considered as being contraindicated. — *K. Aagaard* had the impression that the employment of chloromycetin is rather widespread, while the use of the preparation is actually indicated only in the treatment of typhoid fever. The possibilities of treatment in aplastic anaemia comprise: repeated transfusions, cortisone, vitamin B_{12} and X-ray treatment of the bone-marrow (to prevent the formation of antibodies which frequently occur following repeated transfusions even though complete compatibility is present).

Wilh. Antonsen: **Multiple epiphyseal dysplasiae.**

A case of multiple epiphyseal changes was recorded. The patient was a girl aged 13 years in whom all the epiphyses were altered and deformed as is seen in dysplasia epiphysealis multiplex. In addition to the changes mentioned, severe disturbances of the ossification in the spine were present. The differential diagnosis was discussed.

J. Vesterdal: **A case of Caffey's syndrome.**

This patient was described at a meeting of the Society on Oct. 12, 1955. The patient, a girl, now aged 4½, was healthy during the first year of life, but thereafter she became tired and irritable and developed tenderness of the extremities and had difficulty in walking. X-ray examination revealed singular cortical thickening of the diaphyses of the long bones, particularly of the tibia and fibula and in some short bones, particularly both second metacarpal bones. In some of the metaphyses and epiphyses clear areas suggestive of leukemia were found. The ESR was greatly raised (up to 112 mm). For a period the blood phosphorus was raised (up to 7.8 mg%), while the serum calcium and phosphatase were normal. The serum protein was 7.3 per cent with increase of α_2 and β-globulin. Other blood investigations rendered normal results. Wassermann negative. The disease regressed gradually at the age of 4 years. The ESR is now approximately normal and the changes in the bones have practically disappeared. The gait is normal and there is no tenderness of the extremities. It is now considered that this is a case of the late form of Caffey's syndrome (the pronounced changes of the mandible present in the early cases were absent in this case).

N. J. Schierbeck: **Cases from practice for diagnosis.**

Five patients were mentioned, 3 from the past 14 days, with a *disease resembling exanthema subitum*. The symptoms were marked pyrexia for 3–4 days, some redness in the throat, no swelling of the glands in the neck, fall in temperature by crisis and thereafter a reddish exanthema, marked in the face and in pale patches on the trunk and limbs. There was no demonstrable possibility of a drug exanthema. It is interesting that children aged 9–10 years were involved. Two out of the last three children had had definite rubeola, but none of them are known to have had exanthema subitum.

Discussion.—*P. Drucker, P. W. Bræstrup, T. Iversen, A. Henriques, and B. Friis-Hansen* mentioned that they had all seen one or more cases which resembled those described. The diagnosis was not elucidated in these cases either.

Meeting, October 30, 1957

E. Ryssing: **A case of staphylococcal pneumonia.**

A case of staphylococcal pneumonia occurring in a girl aged 7 years, probably as a complication of influenza was reported. The disease ran a fatal course despite early institution of treatment with sodium penicillin and erythromycin intravenously in massive doses of 24 million units and 2100 mg, respectively, during the course of 34 hours. Blood transfusions, infusion of noradrenalin, chlorpromazine, gamma globulin, 550 mg Actocortin intravenously and 300 mg Cortone intramuscularly were also given. At autopsy, growth of *Staphylococcus aureus* could still be demonstrated in the lungs. The necessity of early bacteriological diagnosis with determination of resistance by

culture from the upper respiratory tract and possible pleural puncture is emphasized. Rapid institution of potent antibiotic therapy with penicillin and bacitracin and/or erythromycin is essential, in addition to gamma globulin, antitoxin and intensive treatment for shock.

Henning Andersen: **Recent concepts concerning the function and diseases of the thyroid gland.**

It must now be assumed that various hormones or hormone fractions are formed in the thyroid gland with more or less specific effects upon the numerous metabolic processes which are dependent upon the thyroid function. Further, increased knowledge has been obtained of the enzymatic processes by means of which iodine and protein compounds are synthesized to hormones and of the function of the thyrotrophic hormone. One of the most important questions in thyroid research is the fractioning of hormones and the elucidation of the mode of action of the individual fractions. A possibility is thereby opened for the understanding of the variations in the clinical picture of thyroid disease from the variations in the hormone pattern in the individual patients, analogous to conditions in disease of the suprarenal glands. On the other hand, it has become apparent that the function of the thyroid plays a rôle in diseases which are not, as a rule, regarded as diseases of the thyroid gland and in which various effects of thyroid would be of therapeutic interest, while others, e.g. the effect upon oxygen absorption and minute volume, are undesirable. As examples of such conditions, investigated in man and in experimental animals, may be mentioned radiation lesions, certain forms of cancer, schizophrenia and experimental alcoholism in rats.

The incidence of *hyperthyroidism* is stated to be approximately 0.01 per cent. Approximately 60 per cent of the cases occur in the age group 10–15 years. Girls are more frequently affected. In an extensive material, goitre was found in 80 per cent, tachycardia in 50 per cent and raised basal metabolic rate in 35 per cent. Accelerated growth in length does not become apparent until the condition has been present for approximately 6 months. In doubtful cases the diagnosis may be established by determination of protein-bound iodine and by administration of iodine isotopes. The therapy is very debatable. Trial of medical treatment according to current principles for adults is advised first. This treatment may possibly be supplemented with Thyroidin in the cases in which an euthyroid state cannot be obtained by medical measures, in patients who do not tolerate antithyroid preparations or who do not co-operate well, and in all cases in which the thyroid is nodular. The author reports 6 cases of hyperthyroidism treated personally.

According to the latest accounts, particularly those from the U.S.A., cases of *nodular goitre* in children should be subjected to operation on account of the risk of malignancy. Four of the author's own cases are mentioned.

The etiology of *hypothyroidism* was as follows in 34 children investigated in Queen Louise's Hospital for Children, Copenhagen: 6 were probably due to disturbance of hypophyseal function, 7 to ectopic sublingual hypoplasia of the thyroid, 8 to hypoplastic thyroid tissue in the normal position, 7 were cases of athyreosis, and 6 cases were associated with goitre, probably compensatory in nature on account of various disturbances in the hormone synthesis in the thyroid. The various clinical pictures, particularly those of the insidious forms, are reviewed. The reader is referred to previous works concerning hypothyroidism (*Nordisk Medicin, 58:* 1282, 1957). Attention is drawn to the fact that some children born without thyroid tissue showed, at birth,

retardation in the growth of bones indicating that they had been inadequately supplied with thyroid tissue in utero. In this connection, the author mentioned his own investigations concerning fetal thyroid function. It appears that absorption of iodine commences in the 12th–13th weeks of pregnancy together with the formation of follicles.

Discussion.—*Bent Andersen* sought further elucidation of the connection between myxedema and deafness. — *Henning Andersen:* No definite explanation of the connection between deafness and congenital myxedema is available. Changes in the mucopolysaccharides in the inner ear may be responsible. We have four patients of this type. — *Jacob Øster* drew attention to the possible connection between cancer of the thyroid and radiation therapy of the organs in the neck. — *Henning Andersen:* It is correct that previous therapeutic irradiation of the organs in the neck is considered to be one of the causes of the increasing number of cases of cancer of the thyroid in children. — *H. Dyggve* inquired about the value of estimation of protein-bound iodine. — *Henning Andersen:* Protein-bound iodine is a good, but not always adequate, measure of the function of the thyroid gland. Still more fractionizing methods are required. — *R. Wichmann* mentioned 2 cases of congenital goitre in siblings. Since the age of 12 years the mother had had a goitre which had required surgical treatment on two occasions with only transient improvement. Clinically she was, however, always euthyroid and never received iodine, thyroid hormone, antithyroid preparations nor radiological treatment. She had undergone 3 uncomplicated pregnancies. The first child, a girl, born in 1947, was normal. The second and third children, who were boys, were born at term, but both were hospitalized immediately after birth on account of congenital goitre. In both cases the goitre was of soft, uniform consistence, somewhat asymmetrical, but involving the entire gland and associated with pronounced compression symptoms (dyspnea, intermittent cyanosis and in the second case dysphagia and a considerably enlarged heart). In both cases the goitre disappeared without treatment in the course of weeks. No definite sign of either hypo- or hyperthyroidism was found in the children, and they have developed normally. In the cases quoted, the development of goitre both in the mother and in the children is presumed to be connected with increased secretion of thyrotropic hormone in the mother, possibly accentuated by insufficient supply of iodine to the mother during the pregnancies.

The majority of cases of congenital goitre are said to disappear spontaneously in the course of weeks or months. Administration of iodine may delay the diagnosis of possible complicating hypothyroidism. The administration of thyroxin has rendered immediate effect in isolated cases. Radiation therapy is not recommended. Cases with compression symptoms produced by congenital goitre have demanded more active surgical therapy. In several of the cases published in the literature, the congenital goitre was of malignant nature. — *Henning Andersen:* In some cases the congenital goitre appears to be due to a hereditary defect in hormone synthesis. The gland undergoes hypertrophy during periods when the thyroid requirement is particularly great, e.g. during the neonatal period or at puberty. H. A. has seen a similar patient in whom the goitre disappeared spontaneously.

Meeting, November 20, 1957

Acting Senior Inspector Holger Horsten: **Current problems in child welfare.**

An account is given of the alterations in the legal administration of Child Welfare in Denmark which must probably be carried out in order to fulfill the decisions in the

Constitution § 70, Part 6, concerning access to trial in court in cases of administrative withdrawal of freedom. Profound disagreement has been expressed concerning to what extent the removal of a child from the parental home must be regarded as "withdrawal of freedom" in the sense of the Constitution. It is very probable that access to trial in court will be retained. A special court may be established for this purpose or the cases may still be brought to the ordinary courts, in which case probably to the higher courts.

In the Memorandum issued by the Administrative Commission of the Ministry for Social Affairs, it was proposed that the Boards for Child Welfare be maintained in their present form as the first authority. Further, it was proposed that the Boards should seek psychiatric and psychological advice. It was proposed that the parents should retain their responsibility in cases where a child is voluntarily removed from the parental home for care. In order to ensure a professionally more rational distribution of children to the various homes with the object of creating the best possible environment for the children with the necessary respect for the pedagogic environment in the various homes, it is proposed that the permission of the Senior Inspector to place children in institutions for difficult or backward children should normally be required in the future *prior* to admission. Further, other problems are mentioned in connection with the future central national administration of Child Welfare. The Minister for Social Affairs has proposed that a comprehensive new law concerning Child Welfare taking effect from April 1st, 1958, shall be carried out. Finally, an account is given of the situation as regards accommodation in homes for children. Simultaneously with the fact that fewer children are now involved in the administration of Child Welfare it has, however, been noticeable that the children actually involved are frequently more difficult than previously and the requirement for further homes for treatment of children and young people with particular difficulties in adaptation is a current problem. It will also be of great significance for the future organisation of Child Welfare if the very necessary research work could be commenced.

Discussion.—*Vagn Christensen* presents an estimated account concerning the possibilities of treatment in a pediatric department for children with nervous disturbances, difficulties in adaptation and other symptoms of disturbed development. The material comprizes 150 patients. Half of the material is estimated to have received adequate treatment. The remaining half could be divided into two groups: (1) Where approximately one third of the clientèle were concerned, possibilities of contact with the family, such as, for example, out-patient control, supervision in the home, the offering of financial assistance from public sources, psychiatric investigation and possibly treatment, etc., were not available. (2) As regards 10–15 per cent of the clientèle, no suitable places for care of the child were available, particularly no suitable foster homes or residential schools for children with predominantly environmental disturbances. To a lesser extent homes for actual treatment were required. — *A. Rothe-Meyer:* A similar investigation is being undertaken in the Hospital for Children, Fuglebakken, Frederiksberg. The speaker has the impression that the difficulties there will prove to be greater than they appear to be in the Copenhagen County Hospital in Gentofte. — *E. Gjørup:* The activity of Child Welfare organisations in recent years has swung somewhat away from care in institutions and towards care in the home, and this must be regarded as satisfactory. The future advisory clinics should be organized as *family* advisory units and with the possibility of offering financial assistance to the family. — *K. Biering-Sørensen* proposes that it should be made possible to place siblings together in the same institution. The risk of infection from a toddlers' ward to an infants' ward is of no signifi-

cance. — *Sv. Heinild:* Behaviour difficulties are not infrequently transient in nature, and it is not always necessary to seek professional advice to overcome these difficulties. — *P. W. Brœstrup* asked if the ordinary organisation for the supervision of children is utilized sufficiently and if it is undertaken by qualified personnel. He recommended that advisory clinics be associated with pediatric departments, in which contact with the parents had been established. The parents frequently default if they are referred to a new place, and the entire case must be reviewed again. — *J. Egsgaard:* There may be considerable differences in the clientèle. The speaker recommends advisory clinics in pediatric departments for the slighter cases and clinics in departments for child psychiatry for the more severe cases.

H. Kreutzfeldt, Copenhagen

Meeting, February 19, 1958

***H. Dyggve and C. E. Gudbjerg:* Bronchiectasis in children.**

(To be published in *Acta pædiatrica* 1958.)

In a re-examination of 17 children who were between the ages of 5 and 15 years when they were operated on for bronchiectasis, we found that one patient was dead, 4 were better than before operation and 12 were symptom-free. The time of observation varied between 12 and 87 months, an average of ca. 4 ½ years. Etiological relationships, symptoms and the roentgen diagnosis are discussed. Post-operative bronchography was carried out in 12 of the patients. There were completely normal bronchograms on both sides in only 7 of the patients. In one of those patients whose parents were opposed to post-operative bronchography, the regular X-ray pictures of the thorax showed that there were still changes on the non-operated side, but the patient had no clinical symptoms 2 ½ years after operation. The prevalance of the disease and the operative and post-operative treatment are discussed. The results are on a level with the best which have hitherto been published. Since there has been described definite regression of light cases, expectant waiting under very close follow-up is sufficient in these cases, whereas early operation is strongly indicated in outspoken cases where the bronchiectasis is not too diffusely spread out. The prophylaxis consists especially in energetic treatment of atelectases, especially when these are combined with infection. Such patients should be treated by bronchoscopic aspiration, physiological respiratory treatment and antibiotics until the symptoms have disappeared and the X-ray of the lungs is negative.

Discussion.— *E. Thamdrup:* Bronchiectases are often unfortunately bilateral and therefore as a rule not operable. There is frequent relationship between recurrent sinusitis and bronchiectasis. The case which was combined with liver cirrhosis, was it examined for pancreatic fibrosis? Hepatic cirrhosis is a frequent finding in autopsies on children dying of pancreatic fibrosis. — *Fr. Therkelsen:* I would have liked to have the etiology a little more completely discussed, especially in reference to whether some of the bronchiectasis cases could have been congenital (bilateral, no known pneumonia cases, etc.). I agree, however, that by far the largest causative factor is atelectasis with pneumonia in the young age groups. I want to stress that pre-operatively with postural drainage and antibiotics given for a longer time one can reach a significant improvement with greatly decreased amount of expectoration. This improvement

does not last long, however, if the patient is not operated. In those cases of widely-spread bronchiectases, where operation is not indicated, it can be advisable to try to produce improvement periodically with conservative treatment. The spontaneous course of bronchiectasis prior to the introduction of antibiotics was very serious. I strongly warn against not operating in cases with localized processes, for here you have a significant possibility of improving the patient and preventing the process from progressing to more serious forms with larger spread and eventual foetid infection. Operation is also indicated in bilateral isolated processes. — *Vilh. Clausen:* I have the experience that the medical treatment of children with bronchiectasis has resulted in a very significant improvement and freedom from symptoms, even when it is a question of serious cases, but I don't know if the result is permanent in the long run. — *P. Plum:* I would like to know results of conservative treatment. — *H. Dyggve and C. E. Gudbjerg:* I know of only one uncertain case of regression of definite bronchiectasis. All cases of pancreatic fibrosis were excluded from the material. By far the most cases in the material are unilateral.

O. Storm, Fr. Therkelsen, P. A. Gammelgård and J. Vesterdal: **Concerning vascular rings in infants—a cause of stridor.**

After a review of the vascular ring's genesis a discussion of the symptoms and diagnostic methods in this condition is given. Especial weight is laid on roentgenological examination of the thorax and esophagus in infants with stridor, dysphagia and attacks of cyanosis. The authors' material, including 7 operated cases and 1 nonoperated case of vascular ring is presented. The prognosis after operative intervention with resection of the tightened vessel is especially good. (To be published in *Ugeskrift for Læger.*)

Discussion.—*P. Plum:* I wonder if cases of the so-called congenital stridor haven't been vascular rings which have nevertheless gotten along alright. I find it notable that one does not see this finding at autopsy. — *Fr. Therkelsen:* One should be especially attentive about this in order to find them at autopsy.

Birte Höeg Brask: **Rumination, illuminated from a pediatric psychiatric point of view.**

Rumination as a psychological symptom is placed in the group with repetitive motor habits such as rocking and rolling. From a chart material of 45 cases which was gone through, there were 7 cases which had developed during prolonged stays in the hospital. The symptom's psychological function is discussed and explained from the basis of the relationship between mother and child with reference to Lories and Spitz's works. It is suggested that a differentiation between benign and malignant rumination be made depending on the degree of disturbance of contact. Rumination which starts in the home should give reason for a psychological investigation of the mother-child relationship while rumination existing in an institution should be a reminder of insufficient stimuli. The causal treatment should take sight of these relationships and in malignant cases take the form of an intensive contact therapy followed by talks with the mother as prophylaxis against relapse. Pediatricians have a key position in the treatment of the early symptoms in a misadaptation between mother and child and thereby in the prophylaxis of later psychic abnormalities.

Discussion.—*C. Friderichsen:* Monrad has described a case in 1912. The child died — had an encephalitis. At that time there had been only 11 cases described. — *P. Plum:*

I point out that that case which is described was treated in Rigshospitalet according to those principles which the author gave—and with good results. — *P. W. Bræstrup:* I have a tendency to send the children home quickly with respect to the mother-child contact. I believe that many of the cases may have an organic background. — *K. Tolstrup:* Is rumination more frequent in boys than in girls? — *B. Hoeg Brask:* There is no certain explanation for the predominance of boys in the material, but that corresponds to the sex ratio for psychiatric diseases later in the pediatric age groups. There are without doubt organic causes behind single cases of rumination, but they are not a satisfactory pathogenetic explanation. Rumination has a psychogenic function in itself. Masturbation belongs just as does rumination to the so-called auto-erotic habits, but is a less primitive form and requires a certain degree of contact with the environment. I agree that ruminative children should be discharged early if, I want to stress, one is sure that a contact has been established with the mother which can continue after discharge. The described emotional substitution therapy is needed in the worse cases, but is of course only the first step in the treatment and should be followed up with a modification of the mother-child relationship if it is this which is pathogenic.

C. C. Winkel Smith: **Some remarks on the question of exploratory laporotomy in children with recurrent abdominal attacks.**

Report of a case of recurrent abdominal attacks in a 10-year-old girl. The attacks were so severe that they caused 4 hospital admissions, twice in the medical division and twice in the surgical division where she underwent laparotomy twice without anything abnormal being demonstrated. At the third laparotomy a right-sided ectopic kidney rudiment was found which could not be seen in the completely normal urography. In connection with this a little review of double-kidney's pathology and clinical features is given. It is further pointed out that gastro-intestinal symptoms predominate in the disease picture where the diagnosis can easily be masked. Finally the necessity is brought out of carrying out exploratory operation in a certain number of these children with recurrent abdominal attacks, even if the clinical examinations show normal relations. A certain guidance can possibly be had by separating out the monosymptomatic cases for themselves, for these so seldom show any organic troubles. In children who have both pains and vomiting and recurrent attacks of fever, however, there can often at operation be shown an organic disturbance, even if the clinical examinations prior to that have given no basis for this. (To be published in *Ugeskrift for Læger.*)

Discussion.—*V. A. Gammelgård:* I think that exploratory laparotomy gives restricted information when one does not previously have a basis for the diagnosis. Exploratory laparotomy should be a last resort which should become less and less used. — *C. C. Winkel Smith:* I think that this standpoint is principally wrong. Naturally, it is desirable to have an exact diagnosis prior to operation. One should only remember that our X-ray diagnosis lets us down. That has been shown to be the case here with urography, and it failed also with respect to the small intestine. One is therefore forced in a certain number of instances to do exploratory laparotomy. That can be done carefully and does not need to be harmful for the children.

Section for Pediatrics and School Hygiene of the Swedish Medical Society

Meeting, February 14, 1958

Y. Larsson: **Tolbutamide treatment in juvenile diabetes.**

After a short review of different theories concerning the mechanism of action of the sulfa-urea combinations, an account is given of the results of attempt at treatment with tolbutamide in 24 cases of juvenile diabetes. In newly-ill patients an early simultaneous use of tolbutamide-insulin treatment together with dietary restriction resulted in such a marked decrease in insulin need that the insulin dosage in most of the cases could be completely discontinued or reduced to a minimum insulin addition only every 2nd to every 4th day. If tolbutamide was given without such "insulin protection" or in a later stage of the disease, no definite effect was obtained. In a pre-diabetic patient a normalization of a "diabetic" glucose tolerance was obtained after two weeks treatment with tolbutamide. Because of the observations' preliminary character it is still too early to definitely define the value of tolbutamide treatment in juvenile diabetes. However, the entirely negative attitude which has appeared in a large number of earlier works does not appear to be warranted. No side effects of treatment were observed.

Discussion.—*G. Engleson* started more than two years ago with BZ 55 in juvenile diabetes. The best result and agreeing with Yngve Larsson's has been obtained with a combined diet-insulin-tolbutamide treatment in fresh cases. Patients are however not allowed to continue with tolbutamide because of the risks for toxic effects. One obtains in the initial stage a considerably reduced insulin need in a combined treatment, and that can be maintained for a long time through careful dieting and insulin. The possibility of "late failures" in long-term treatment with tolbutamide should be watched for. In several cases an increase in the alkaline phosphatase was observed and it is probable that the tolbutamide effect is mediated by influence, among other things, on liver function (enzyme system) which urges care in protracted treatment.

C. G. Bergstrand and E. Odeblad: **Uterine measurements in children.**

(Published in *Acta pædiatrica* 1958.)

A. Lundberg: **Paroxysmal tachycardia in infants.**

Paroxysmal tachycardia in infants is an important disease, because undiagnosed it can lead to death, but when noticed constitutes a thankful object for therapy. Among infants who die with unclear asphyxia, it can be suspected that cases of paroxysmal tachycardia are hidden. A heart rate which is so fast that it cannot be counted with a stethoscope should occasion an ECG which easily gives the diagnosis and differentiates between paroxysmal atrial tachycardia and ventricular tachycardia, flutter or fibrillation—conditions which are more seldom and not touched on here. Those cases, which during the attack have short intervals of normal cardiac rhythm, can during the free interval be revealed by a WPW syndrome, which in more than half the cases appears in the ECG during the run of normal rhythm. That discovery in an asphyctic infant should motivate careful controls of the pulse during the following hours to definitely

establish the diagnosis. The treatment is medical. Vagus irritation in the form of straining, vomiting reflex, eyeball pressure and carotid massage are inappropriate in these small children and do not lead to the goal in contrast to the situation in older children and adults. Firstly, digitalis should be used; the long-acting digitoxin with cumulative effect given by mouth has a good result within 24 hours in those 3 cases which were taken care of during the past year at Kronprinsessan Lovisas Barnsjukhus. For the next month after the attack digitalis is given in maintenance dose with the aim of preventing recurrence. Recurrences are infrequent in children whose paroxysmal tachycardia makes its debut during the first half year of life, as differentiated from the older childrens' recurrent attacks up to adult age.

B. Karlsson: **"Madelung's deformity".**

A lower arm deformity of Madelung's type is described in 14 patients who are distributed among two families. The viewpoints which are presented concerning Madelung's deformity are in agreement with the earlier observations of the Norwegian Bernhard Paus. From the etiological standpoint the deformity in the two families can be ascribed to an autosomal dominant inherited factor. From a pathogenetic standpoint the development of the lower arm deformity is not primarily determined by a premature closure of the epiphysis volar-ulnar in the distal radial disc. Madelung's deformity is regarded as a partial symptom in a more general skeletal affection with general growth retardation of a disproportional type. The growth retardation is discernible above all in the lower arms and lower legs and radiographic changes have here also been observed in the lower legs, which is not thought to be found described earlier. The growth retardation can manifest itself before the lower arm deformity has developed, which is illustrated by at least one case. That Madelung's deformity is a partial symptom in a more general skeletal affection is illustrated to a certain degree also in that all afflicted individuals show an obviously uniform type of constitution. Certain likenesses are present with the disproportional dwarf growth in chondrodystrophia foetalis. In that affection the growth retardation is, however, most pronounced in the upper arms and femurs. In Madelung's deformity it is most pronounced in the lower arms and lower legs.

O. Qvist: **Testicular tumors in children.**

Testicular tumors in children are not common. At Kronprinsessan Lovisas Barnsjukhus 8 cases, of which 3 were malignant, have been operated on in 12 years. The other 5 cases consisted of dermoid cysts and benign teratomas. The treatment consisted in all cases of testicular excision, in 1 case followed by inguinal node dissection and post-operative radiation. All cases are alive and well with the shortest observation time being 3 years with regard to the malignant tumors. The differential diagnosis between testicular tumors and scrotal swelling of other cause in children is generally not difficult. A hydrocele can be secondary to a tumor originating in the testis or the tunic vaginalis.

C. Thoren: **Cardiopathy in Friedrich's ataxia.**

A family from the Stockholm island region is described. In the family a marriage of cousins plus an even closer in-marriage (uncle-niece) resulted in 5 and 2 children respectively. In the first family 2 boys have Friedreich's ataxia with marked signs of cardiopathy. In the older child it has been possible to follow the ECG since the first

tracing 13 years ago at which time it was normal. First after several years came the typical inversion of T_{II} and T_{III}. Since then there has occurred a progressive return to normal T-waves while the electrical axis has become progressively more deviated to the right. The other brother does not have fully typical ECG changes, but has a pathological murmur and cardiac enlargement. A 14-year-old brother of these two also has a murmur and cardiac enlargement. His ECG shows incomplete right bundle branch block plus an ectopic atrial discharge center. His neurological status is entirely negative, however. An 8-year-old sister has no murmur or heart enlargement, but ECG shows right axis deviation (+ 100°) plus a right-sided intraventricular conduction disturbance. Similar changes have earlier been described as suspicious of Friedreich's ataxia. These two last-mentioned siblings are, therefore, strongly suspected of having an isolated cardiopathy. The other family has two boys, 9 and 7 years old. Both have Friedreich's ataxia. The older boy's neurological symptoms began at about age 7 years, but the diagnosis could first be made after the ECG showed typical changes with deep, negative T in Leads II, III, V_4–V_6 and VF. Following exercise there was further accentuation of the changes as well as negative T_I. Blood volume as well as total hemoglobin are elevated. A loud murmur and cardiac enlargement are also present. Of the serum enzyme profile, transaminase and malic dehydrogenase have shown normal values while lactic dehydrogenase has been elevated (LD 34 and 43 units), pointing to an active muscular degeneration. The younger brother's neurological symptoms consist only of areflexia in the legs. His ECG is clearly pathological, however, and X-ray shows a slight cardiac enlargement.

Acta Pædiatrica **47**: 478. July 1958

BOOK REVIEW

Moderne Probleme der Pädiatrie · Problèmes Actuels de Pédiatrie · Modern Problems in Pediatrics, Vol. III. Bibliotheca Pædiatrica, Fasc. 66.

S. Karger A. G., Basel, 1957. XVI + 592 pp., 126 figures. Price Swiss fr. 96.00.

The third volume of *Modern Problems in Pediatrics* is devoted to two different fields, where important advances have recently been made. One concerns autoimmunization as a pathogenic principle and the other the inborn errors of metabolism and related conditions. The former includes diseases caused by an immunologic mechanism affecting the red cells with resulting different types of hemolytic anemias, the white cells leading to leukopenia and agranulocytosis, the platelets with a consequent hemorrhagic disorder. Also, other bleeding diseases based on an immunological cause are dealt with, and this first part of the volume ends with immunological aspects of rheumatic diseases and nephritis. The latter part covers many of the congenital and familial metabolic disturbances known, and although several of them are rare, they offer a fascinating opportunity for metabolic studies, where in many instances the exact defect in an enzyme system can be localized and genetically traced. In this part of the book congenital porphyria, abnormal hemoglobins, abnormal metabolism of iron, Wilson's disease, disturbances of the metabolism of different amino acids including Fölling's disease, disturbances of pigmentation, oxalosis, gout, glycogen storage diseases, galactosemia, abnormal metabolism of fat and inorganic phosphorus, hypercalcemia, marble bone disease, primary metabolic acidosis and congenital alcalosis are described. The authors of the various chapters are all outstanding specialists in their respective fields and several of them have contributed substantially to the advances made. Some of the papers are original communications, others have more the character of a review of that special topic. The quality of the papers with their extensive bibliographies will enable the pediatric practitioner as well as the specialized research worker to get a concentrated and reliable presentation of the disorder in question. The editors are to be congratulated on their successful efforts in bringing the views and experience of so many experts together in this book. It ranks high among the volumes of this series and also among other classical works dealing with recent advances and trends in pediatrics.

B. Hellström

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Aus dem Institut für Mikrobiologie und Immunologie, der Rheumatologischen Abteilung, Infektionsabteilung und Kinderabteilung der Universitätsklinik in Pilsen

Die Beziehung der Antistreptohyaluronidase zur immunologischen Reaktivität bei akutem Gelenkrheumatismus[1]

von VLADIMÍR ZAVÁZAL, JOSEF LAVIČKA, JOSEF WEIDENHOFER, VÁCLAV DORT und EVA BOŘÍKOVÁ

Die Ermittlung des Titers der Antistreptohyaluronidase (ASH) wird bei rheumatischen Krankheiten als eine diagnostische Methode bei akutem Gelenkrheumatismus verwendet. Wenn man auch eine direkte Beziehung der ASH-Titerhöhe zur Aktivität des pathologischen Prozesses statistisch nachweisen kann, dauern bei fast der Hälfte der Rheumatiker die hohen ASH-Werte auch nach Erlöschen des Prozesses oft lange bis in die Rekonvaleszenz hinein an. Wir stellten uns die Frage, ob vielleicht der ASH-Titer eher die immunologische Reaktivität zu einem der Streptokokkenantigene als die Aktivität des pathologischen Prozesses ausdrückt (1, 7). Wir verfolgten darum die Beziehung der durch inkomplette Antikörper nach einmaligem Brucellaantigenimpuls gemessenen immunologischen Reaktivität zur ASH-Titerhöhe in der Rekonvaleszenz der Streptokokkeninfektion und des akuten Rheumatismus.

Material und Methoden

Gruppe 1 bestand aus 10jährigen Kindern, welche 8 Tage mit Scharlach isoliert und mit Penicillin behandelt worden waren. Bei der Entlassung wurde der Antigenimpuls durchgeführt und 14 Tage später ein Blutmuster zur Untersuchung der immunologischen Reaktivität und ASH entnommen. Bei keinem Kind wurden in dieser Zeit Komplikationen festgestellt.

Gruppe 2 bestand aus 14jährigen Knaben, welche eine unbehandelte Streptokokkeninfektion der oberen Luftwege durchgemacht hatten und in der Zeit der Untersuchung, also 7–14 Tage nach der Infektion, noch beta-hämolytische Streptokokken in den oberen Luftwegen trugen. In der Zeit der bakteriologischen Untersuchung wurde der Antigenimpuls durchgeführt und nach 14 Tagen wieder das Blut untersucht.

Gruppe 3 bestand aus Kindern von 6 bis 14 Jahren, welche nach Durchmachung des akuten Rheumatismus 3 Monate bis 2 Jahre unter klinischer Kontrolle standen.

[1] Statistische Mitarbeit: Vladimír Malý. Technische Mitarbeit: Jiřina Čapková.

TABELLE 1

Die Beziehung der inkompletten Antikörper nach einmaligem Brucellaantigenimpuls zur Antistreptohyaluronidase bei Scharlachrekonvaleszenten.

	Titer der inkompletten Antikörper									
ASH-Titer	0	20	40	80	160	320	640	1280	2560	Zusammen
0	2	1		1	1	1	1			7
40	2			2			1			5
80	7	1	3	1	3	1	1	1		18
160	9	2	3	5	6	6	1		1	33
320	6	6	3	2	2	2	1	1		23
640	2	1	1	1	7	3	3			18
1 280				1	4	2	1			8
2 560				1						1
5 120										
10 240								1		1
Zusammen	28	11	10	14	23	15	9	3	1	114

Bei diesen Rekonvaleszenten fanden sich in der Zeit der Untersuchung keine Zeichen der Aktivität des pathologischen Prozesses.

Bei allen Gruppen wurde am Tage der Durchführung des Brucellaantigenimpulses ein Blutmuster zur Kontrolluntersuchung der kompletten und inkompletten Brucellaantikörper entnommen. Bei allen Untersuchten gab diese Kontrolluntersuchung ein negatives Ergebnis. Die Methodik der Durchführung des Antigenimpulses und der serologischen Bestimmung der immunologischen Reaktivität wurde in einer früheren Mitteilung beschrieben (8). Die Antistreptohyaluronidase wurde durch „MCP-Test" in der Modifikation nach Harris festgestellt (2).

Ergebnisse

Die gleichzeitigen Resultate der inkompletten Antikörper nach dem Brucellaantigenimpuls und der Antistreptohyaluronidase haben wir für die einzelnen Gruppen in Korrelationstabellen zusammengestellt.

In der Tabelle 1 führen wir die Ergebnisse bei Gruppe 1 an. Es wurde festgestellt, dass zwischen beiden Reaktionen eine statistische direkte Korrelation nachgewiesen werden kann ($r = 0{,}24$).

In der zweiten Tabelle finden sich die Resultate bei der Gruppe der Knaben, die eine unbehandelte Streptokokkeninfektion durchgemacht haben. Hier wurde eine hoch signifikante statistische Beziehung zwischen der Titerhöhe beider Teste gefunden ($r = 0{,}73$).

In der Tabelle 3, sind die Resultate bei der Rekonvaleszenten nach Febris rheumatica angeführt. Auch hier zeigt der Korrelationskoeffizient eine direkte Beziehung der Titer der beiden Reaktionen ($r = 0{,}278$).

TABELLE 2

Die Beziehung der inkompletten Antikörper nach einmaligem Brucellaantigenimpuls zur Antistreptohyaluronidase bei Rekonvaleszenten nach einer unbehandelten Streptokokkeninfektion.

	Titer der inkompletten Antikörper						
ASH-Titer	80	160	320	640	1280	2560	Zusammen
0							
40			1				1
80		2					2
160	1	3	2	2			8
320			3	3	3		9
640				4	4		8
1280					2		2
Zusammen	1	5	6	9	9		30

TABELLE 3

Die Beziehung der inkompletten Antikörper nach einmaligem Brucellaantigenimpuls zur Antistreptohyaluronidase bei Rekonvaleszenten nach akutem Gelenkrheumatismus.

	Titer der inkompletten Antikörper											
ASH-Titer	0	20	40	80	160	320	640	1280	2560	5120	10240	Zusammen
0												
40						1						1
80					1	1	1					3
160				1		1	4	2	1			9
320					1	1	2	3	2			9
640		1					1	2	2	3	1	10
1 280					1		3			1	4	9
2 560							3	2	1			6
5 120					1			1		1		3
10 240								1				1
Zusammen		1		1	4	4	14	11	6	5	5	51

Diskussion

Die dynamische Verfolgung der immunologischen Reaktivität könnte bestimmt eine beträchtliche Bedeutung nicht nur für die Erforschung der Pathogenese des Rheumatismus sondern auch für dessen Prävention haben. Bisher ist aber keine andere passende Methode zur Bestimmung der immu-

nologischen Reaktivität bekannt als die zum ersten Mal von Wagner u.a. (6) benutzte. Wegen der anamnestischen Reaktion kann man aber diese Methode bei derselben Person nur einmal benützen. Die Befunde der hohen Titerwerte der ASH bei einer Reihe der Rekonvaleszenten nach dem akuten Rheumatismus ohne nachweisbare Aktivität des pathologischen Prozesses oder Streptokokkeninfektion sprachen dafür, dass der ASH-Titer in der Rekonvaleszenz mehr eine Resultante der immunologischen Reaktivität des Organismus als der Aktivität des Prozesses ist. Auch der Inhibitionseinfluss einiger antirheumatischer Medikamente auf die Antigen-Antikörper-Reaktion in vitro, welchen wir früher gerade für inkomplette Antikörper und Antistreptohyaluronidase bewiesen (5), zeugt für einige gemeinsame Eigenschaften beider Systeme. Heutige Befunde in allen Gruppen bestätigen wirklich unsere Voraussetzung besonders dort, wo die untersuchten Personen eine homogene Gruppe, wie z.B. in der Gruppe 2, bildeten.

Aus den angeführten Ergebnissen scheint hervorzugehen, dass die Feststellung der ASH bei rheumatischen Krankheiten ausser dem diagnostischen Sinne eine weitere indirekte Methode zur Messung der immunologischen Reaktivität zu einem wichtigen Streptokokkenantigen bedeuten könnte. Es ist jedoch nötig in Betracht zu ziehen, dass der ASH-Titer nicht nur durch die Reaktivität des Organismus wie bei dem Brucellasystem beeinflusst ist, sondern dass er noch von vielen weiteren Faktoren, besonders von dem Zusammentreffen mit Streptokokken, abhängig ist. Trotzdem denken wir, dass der ASH-Titer wenigstens ein Orientationsbehelf für die Bewertung der immunologischen Reaktivität in der Rekonvaleszenz der Streptoinfektionen und des akuten Rheumatismus sein könnte.

Zusammenfassung

Die Autoren verfolgten die Beziehung der Antistreptohyaluronidase zur immunologischen Reaktivität, gemessen durch inkomplette Antikörper nach einmaligem Brucellaantigenimpuls bei Rekonvaleszenten nach Streptokokkeninfektionen und akutem Gelenkrheumatismus. Sie fanden eine direkte Beziehung der Titerhöhe in beiden Methoden.

The relation of the antistreptohyaluronidase to the immunological reactivity in acute articular rheumatism.

The authors have traced the relationship between antistreptohyaluronidase and immunological reactivity, measured in incomplete antibodies after a single brucella-antigen stimulus, in convalescents from streptococcal infections and acute polyarthritis. They found a direct relationship between the titre values with both methods.

Rapport de l'antistreptohyaluronidase avec la réactivité immunologique dans le rhumatisme articulaire aigu.

Les auteurs se sont efforcés d'établir quelle est la relation qui existe entre le taux de l'antistrepto-hyaluronidase et celui de la réactivité immunologique, mesuré d'après le taux d'anticorps incomplets après une seule inoculation d'antigènes Brucellaires chez des convalescents relevant d'une infection streptococcique ou d'une crise de rhumatisme articulaire aigu. Ils ont constaté que ces deux taux étaient en rapport direct dans les deux cas.

Relación de la antistreptohialuronidasa con la reactividad inmunológica en el reumatismo articular agudo.

Los autores estudiaron la relación de la antiestreptohialuronidasa con la reactividad inmunológica, determinada por la valoración de anticuerpos incompletos después de un estímulo antigénico brucelar único, en convalecientes de infecciones estreptocócicas y de reumatismo articular agudo. Hallaron una relación directa de la titulación en ambos métodos.

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From the Lying-in Hospital of the City of Turku, Finland

Capillary Erection and the Structural Appearance of Fetal and Neonatal Lungs

by S. JÄYKKÄ

Introduction

The atelectatic fetal lung has the appearance of a crumpled sack in which the folded capillary tubes are non-patent within the potential walls of the air spaces. At birth an increase occurs in the flow of blood through the lung which distends the unstrained collapsed capillary bed, i.e. effects capillary erection. Applying this hypothesis Jäykkä (1956) was able to bring about expansion of the fetal lung by forcing liquid into the capillaries through the pulmonary artery. A fetal lung expanded by the liquid pressure in the lung capillaries resembles microscopically a normally expanded lung. The expansion effected in this way is termed erectile expansion to distinguish it from inflation brought about by air introduced through the bronchus.

The bearing of this observation on the blood pressure relationships in prenatal and neonatal life is of considerable interest. James (1957) has claimed that the concept of capillary erection is untenable since the high pulmonary pressure in the fetus should effect erection and lung expansion already before delivery. Also Reynolds has criticized the concept by stating that the reduced blood pressure and increased blood flow when respiration is initiated cannot effect erection of capillaries, for if erection of vessels were to occur, there would necessarily have to be a constriction somewhere in the venous pathway with an increase in pressure and no increase in flow (personal communication).

In his monograph *Die menschliche Lunge* v. Hayek writes that the terminal arteries are closed in the lungs of newborn by a blocking mechanism possibly associated with swelling of epitheloid cells. He also suggests as one prerequisite for the establishment of pulmonary circulation the canalization of the blocked arteries. A sequence of this type seems to be supported by certain observations of Civin and Edwards (1951) and Reynolds (1956). According to the latter writer, the capillaries are visible in the aerated, but

not in the fetal lung. Reynolds is, however, of the opinion that the opening of the capillaries is a passive process that follows the establishment of muscular tone and respiratory movements (personal communication).

If the capillary circulation is not patent in the atelectatic fetal lung, the question arises by what route blood flows through the lungs.

According to v. Hayek, the arterial anastomosis between the pulmonary and bronchial arteries was described by Ruyisch already in 1721. v. Hayek is to be credited for the description of the arterio-venous anastomosis between the bronchial artery and the bronchial venous plexus. v. Hayek's observations have been later confirmed by similar ones made by Castigli (1949), Tobin (1950) and Tondury and Weibel (1956). Hence there does exist a short-circuit system that bypasses the capillary bed. Verloop, however, did not find the arterio-venous anastomosis described by v. Hayek, and he considered it impossible that blood under low pressure in the pulmonary artery could flow against the higher pressure in the bronchial artery. It is, however, a fact that the pulmonary pressure is the higher of the two in the fetus.

In this connection the physiological experiments of Prinzmetall (1948) are illuminating. Glass spheres 100–390 microns in diameter injected into the right ventricle could be recovered from the left side in rabbits, cats and dogs. The same was later demonstrated in isolated human lungs by Tobin & Zariquiey (1950). Since the diameter of a capillary is only 12 microns when distended (v. Hayek), there must be another route of larger diameter by which blood can flow through the lung. Arterio-venous shunts have been observed also in a living guinea pig's lung by Irwin *et al.* (1954).

Besides fetal atelectasis, we encounter strongly aspirated and expanded lungs in stillborn infants. The latter observation raises the question whether the functional circulatory change from the fetal to the adult pattern can take place intrauterinely and lead to capillary erection and lung expansion.

In the present investigation the main points of interest have been the status of the capillary circulation in the fetal atelectatic lung and the response of the circulation to asphyxiation.

Method and Material

The differences in the structural appearance of lungs aerated by erectile expansion and those aerated by inflation have been described previously (Jäykkä 1957). Briefly, a lung expanded by inflation with air only is characterized by large sack-like air spaces with thick walls in the proximal parts, while no expansion has occurred in the distal parts. (Fig. 6.)

A lung expanded by erectile force has a structure of normal appearance which differs from the preceding in the well discernible uniform expansion of the capillary network. (Fig. 10.)

The patent and non-patent capillary structures can be distinguished by customary staining methods, but the difference becomes more strikingly evident if india ink is injected through the pulmonary artery, it being assumed that the injected dye follows the same route as the blood does in vivo. With this purpose I introduced a cannula into the pulmonary artery and injected 20 cc of india ink, which readily entered the lung. The pulmonary veins were not tied. The liquid ran through the lung but left some areas unstained. Pieces of the injected lung were fixed in formalin, embedded in paraffin, and dyed by the van Gieson method.

In this investigation post-mortem lungs have been studied to determine the status of the blood circulation and the corresponding lung structure (type of aeration).

As it is not possible to obtain undisturbed human lung specimens one must be satisfied to examine atelectatic and expanded areas in the lungs of infants that have died pre- and postnatally. However, these latter offer the advantage that the route of the injected dye can be compared in atelectatic, strongly aspirated and expanded, and aerated areas of the same lung.

To obtain comparable material, the asphyxiated lungs were chosen so that the cause of the asphyxiation could be defined with the greatest reliability. The causes were tightly looped cords, prolapsed and compressed cords, and prematurely detached placentae. To obtain additional information on the continuity of the processes examined, the material resulting from asphyxiation has been divided into two groups according to whether the fetus died prior to or after delivery.

A third group of lung specimens comprised those where no signs of asphyxiation were evident. This group consisted of lungs of premature infants that had died neonatally.

In the following the lung specimens examined are described.

I. Lung specimens from asphyxiated fetuses

(a) *Fetuses that had died prior to delivery*

1. Full-term fetus weighing 3850 g. Premature detachment of placenta and four loops of cord tightly wound around the neck. Discolored amniotic fluid. Heart sounds not heard prior to delivery.

   Lungs: Congested. Petechial hemorrhages. Expanded as effected by erectile expansion. Aspirated matter in air spaces.
2. Premature fetus weighing 1250 g. Breech presentation. One loop of cord around the neck. Discolored amniotic fluid. Heart sounds had ceased prior to delivery.

   Lungs: Congested. Petechial hemorrhages. Expanded as by capillary erection. Aspirated matter in air spaces.
3. Full-term fetus weighing 3500 g. The fetus died two days before delivery. One loop of cord tightly wound around the neck. Discolored amniotic fluid.

   Lungs: Congested. Petechial hemorrhages. Expanded as by capillary erection. Aspirated matter in air spaces.
4. Full-term fetus weighing 3100 g. Two loops of cord around the neck. Discolored amniotic fluid. The heart sounds ceased prior to delivery.

   Lungs: Congested. Petechial hemorrhages. Preponderance of fetal atelectasis. Minor areas expanded as by capillary erection. Aspirated matter in air spaces.
5. Full-term fetus weighing 3250 g. Prolapsed cord with true knot. The cord prolapsed 10 minutes before delivery when the fetus was still alive. The fetus was dead when delivered. Discolored amniotic fluid.

Lungs: No congestion or petechial hemorrhages. Under the microscope a preponderance of expanded areas as produced by erectile expansion was seen. The air spaces contained air, aspirated matter and extravasal blood. Few atelectatic areas.

(*b*) *Fetuses asphyxiated during labor but delivered alive*

6. One twin weighing 2750 g. Delivered by Caesarian section. Prolapsed cord. Discolored amniotic fluid. The infant lived three days and died from respiratory distress.

   Lungs: The general appearance is seen in Fig. 5. A preponderance of aerated areas of the inflation type (designated by *3*), small atelectatic areas (*2*), and limited areas expanded as by erectile expansion (*1*) are visible.

7. Infant weighing 2000 g. Prolonged delivery. One loop of cord around the neck. No discolored amniotic fluid was observed. The infant lived eight days and had cyanotic attacks when fed.

   Lungs: Congested and containing numerous petechial hemorrhages. Aerated as by inflation. Hyaline membranes.

8. Infant weighing 3200 g. One loop of the cord was around the neck and one around the shoulders. Discolored amniotic fluid. The infant died from respiratory distress after having lived 14 hours.

   Lungs: Congested with abundant extravasal blood. Expanded throughout as by erectile expansion. The air passages, both bronchioli and alveolar sacs, contained abundant aspirated matter and blood cells.

9. Infant weighing 3200 g. Three loops of cord around the neck. Discolored amniotic fluid. The infant died from severe respiratory distress one day after birth. The infant received accidentally an excess of oxygen while being rocked.

   Lungs: Congestion and petechial hemorrhages. Aerated as by inflation. Bullous emphysema. Air in sheets surrounding the vessels. Hyaline membranes. Small areas expanded as by capillary erection and containing aspirated matter.

II. Premature infants with no signs of fetal asphyxiation

10. Premature infant weighing 1300 g. Delivered by Caesarean section in seventh month of gestation. Lived one day.

    Lungs: Expanded as by inflation. Entries to capillary bed closed. Hyaline membranes. Remnants of fetal atelectasis.

11. Premature infant weighing 1600 g delivered in the sixth month of gestation. The infant lived 12 hours.

    Lungs: preponderance of fetal atelectasis. Minor areas expanded as by capillary erection and entry to capillary bed canalized. A few proximal air spaces aerated as by inflation.

12. Premature infant weighing 1320 g delivered in seventh month of gestation. The infant lived one day.

    Lungs: Aerated as by inflation. Entries to capillary bed closed. Hyaline membranes. Remnants of fetal atelectasis.

13. Premature infant weighing 1550 g delivered in seventh month of gestation. The infant lived 17 hours.

    Lungs: Fetal atelectasis. Closed entries to capillary bed. Air has entered the lung as by inflation. Hyaline membranes.

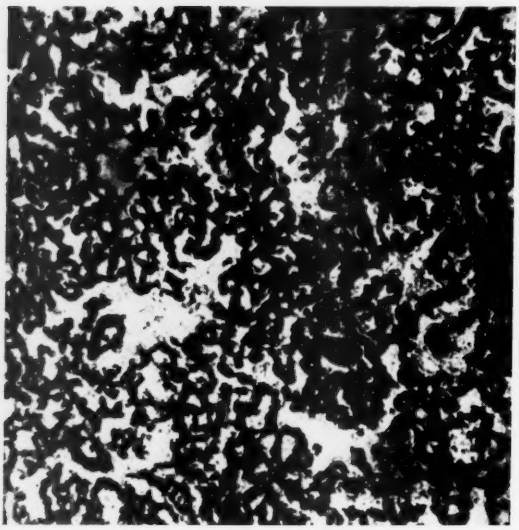

Fig. 1. An atelectatic lung into which india ink has been introduced backwards through the pulmonary vein and which has the "crumpled sack" structure of fetal atelectasis and permits free entry of dye. Magnification about 150 ×.

III. Fetal atelectatic lung specimens

Extensive atelectatic areas were found in the following specimens.

14. Full-term infant weighing 3700 g. The fetus was delivered with forceps in statu medio, twenty minutes after slowing of heart beats was observed as the first sign of asphyxiation. The fetus was dead when delivered. The amniotic fluid was not discolored. The colon contained meconium. No insufflation or other resuscitation procedures were attempted.

    Lungs: Macroscopically atelectatic. Two petechial hemorrhages were seen in the left lung. The microscopical section of the lung (Fig. 2) revealed a preponderance of atelectatic areas. Some air in the proximal air passages. No aspirated matter. Closed entries to capillary bed. Injected dye seen in parts of the short-circuit system bypassing the capillary bed. Veins well filled with India ink.

15. The lung of full term fetus weighing 3700 g. The infant was given oxygen because of persistent cyanosis, but lived only 5 hours. Necropsy revealed diaphragmatic hernia, which had prevented the expansion of the lung. No injection of dye.

    Lungs: Preponderance of atelectasis. Some air had entered the proximal air passages as in air inflation. No aspirated matter visible. Terminal pulmonary arterioles closed. Veins and parts of short-circuit system well filled with blood corpuscles.

Fig. 2. An atelectatic lung lobule into which india ink has been introduced the normal way through the pulmonary artery. The india ink has bypassed the capillaries but entered the interlobular vein and pleural network. Magnification about 50 ×. (A) A detail of the pleural vessels in the lung; (B) a detail of the submucosal venous plexus of a bronchiole showing the route of injected india ink; (C) a detail of the submucosal venous plexus of a bronchus showing the route of injected india ink from the pulmonary artery to the submucosal veins of the bronchus. Magnification in (A), (B) and (C) about 150 ×.

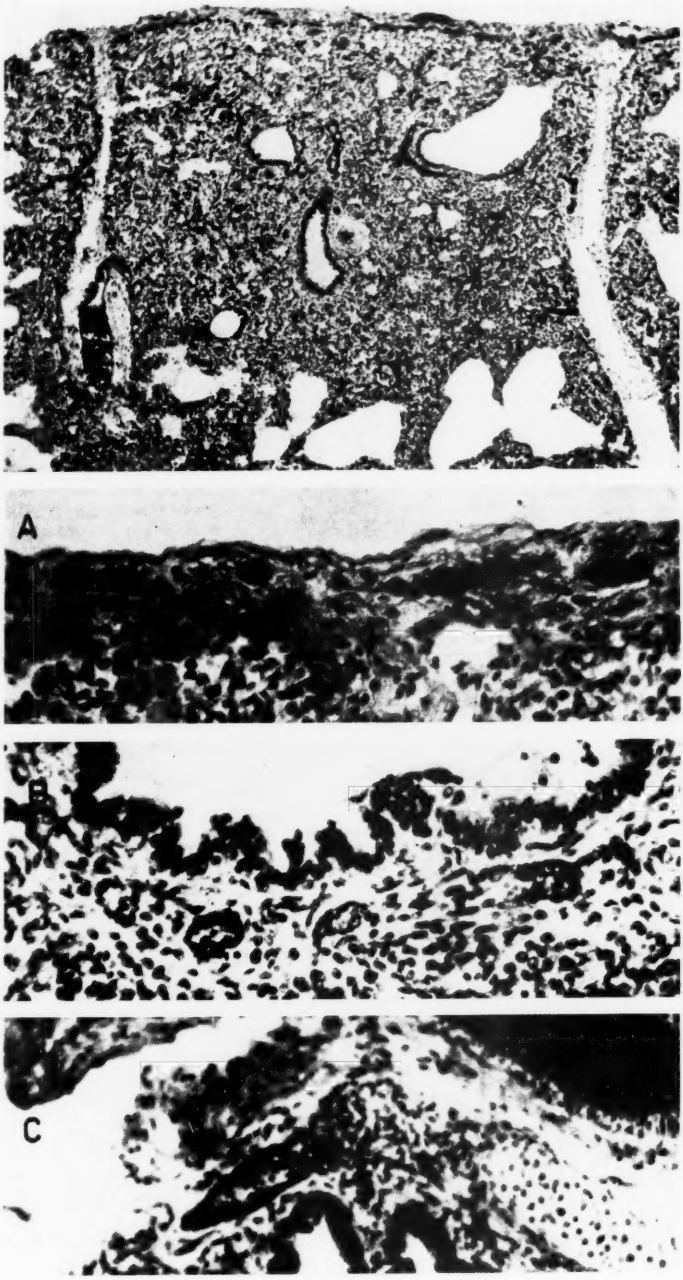

Fig. 2.

Fig. 3. Arterio-venous anastomosis. A longitudinal section through a bronchus (*Br*) showing the inside wall of the bronchus, transverse muscle fibres and part of the epithelium. India ink injected into the pulmonary artery has passed the arteriovenous anastomosis and entered the submucosal venous plexus that drains into the pulmonary vein. Magnification about 150 ×.

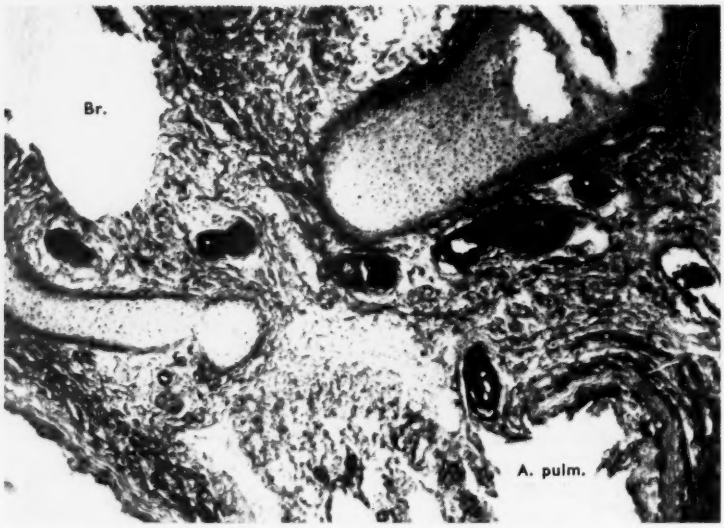

Fig. 4. Arterio-venous anastomosis in the same lung (Fig. 3). A transverse section. Magnification about 150 ×.

Results

The status of the circulation in fetal atelectatic areas

When dye is injected into the lung through the pulmonary vein, it readily permeates the capillary bed completely (Fig. 1).

When, however, the injection is made through the pulmonary artery, the dye bypasses the capillary bed in atelectatic areas although it passes through the lung. The dye can be found in the parts of the short-circuit system described by v. Hayek. (Figs. 2, 3 and 4.)

The same status is seen in lungs of prematures with no signs of asphyxiation.

The lungs of infants that had died neonatally revealed closed entries to the capillary bed on the arterial side in remnants of atelectatic areas. If air has been introduced into the lung by artificial resuscitation or by the infant's own respiratory efforts a structure resembling that produced by inflation will be seen. (Figs. 5 and 6.)

The thick walls separating the inflated air spaces remain in the atelectatic state. Hyperexpansion may occur and may lead to bullous emphysema. Injected dye does not enter the capillaries except possibly an isolated capillary here and there which parallels the curvature of the expanded air spaces.

This type of aeration has been previously described by Potter who stated it to result from artificial resuscitation procedures or from respiratory efforts in prematures weighing less than 2000 g. Kaufman & Spiro have described the same condition and have called it congenital alveolar dysplasia. I have found that this type of aeration can be produced experimentally by blowing air through the bronchus into an atelectatic lung specimen in which capillary erection has not occurred.

The atelectasis associated with the much-discussed hyaline membranes responds to injection of dye in the same manner as described above. The entries to the capillaries still remain closed. The dye appears in the bronchial arteries, submucosal venous plexus and in the veins, but not in the capillaries. (Figs. 7, 8 and 9.)

It is difficult to understand, however, how the congested capillaries become filled in vivo from the arterial side, since it is very difficult to force dye past the closed entries to the capillaries. It is possible, however, that the capillaries become filled in a reverse manner through the arterio-venous anastomosis.

Thus, injected dye does not gain access to the capillary bed in atelectatic areas, firstly, in specimens of lungs of infants that have died prior to delivery, secondly, in lung specimens aerated as by inflation in infants that have died neonatally and, thirdly, in hyaline membrane lungs.

The air has not opened the entry to the capillary bed in the inflation type of lung. The status has evidently been maintained through delivery and capillary erection has not taken place.

Fig. 5. Respiratory distress. India ink was injected into both pulmonary arteries. For the explanation of areas numbered *1–3*, see text.

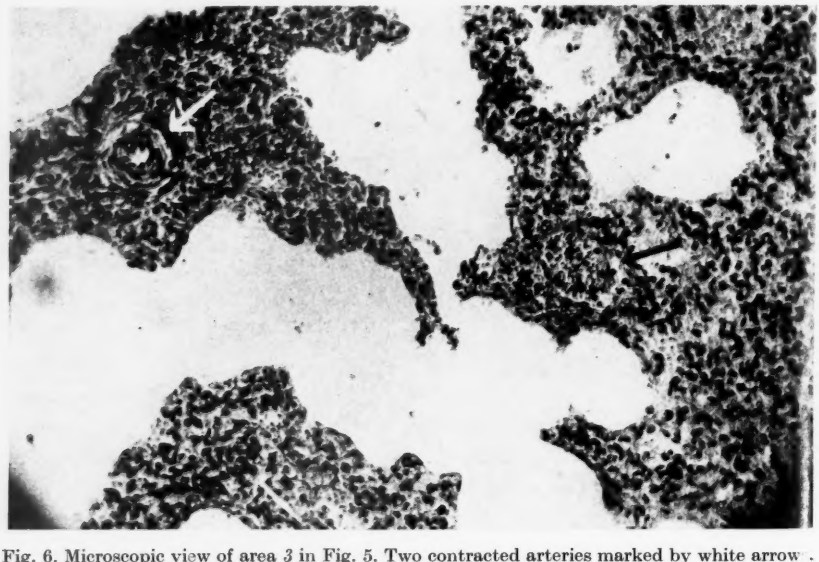

Fig. 6. Microscopic view of area *3* in Fig. 5. Two contracted arteries marked by white arrow. The endothelial nuclei are erect. A vein filled with blood corpuscles is marked by a black arrow. Globular sacklike hyperdistended proximal air spaces; distal air spaces unexpanded (compare Fig. 10). Magnification about 150 ×.

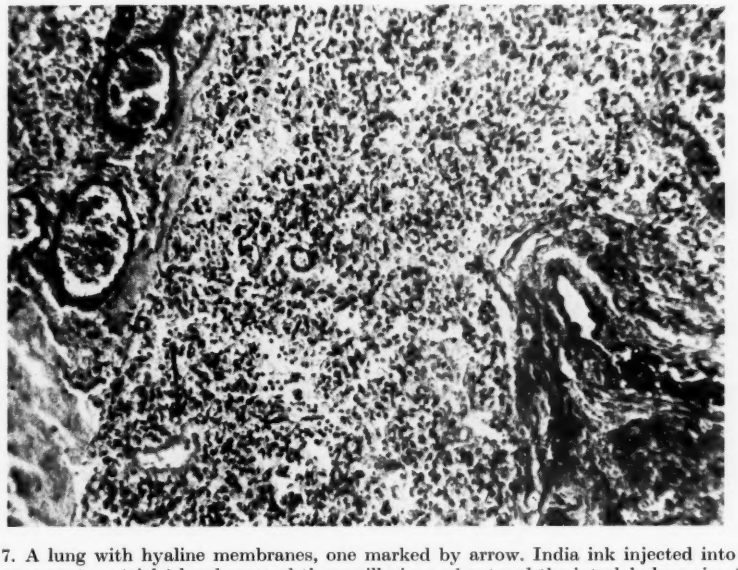

Fig. 7. A lung with hyaline membranes, one marked by arrow. India ink injected into the pulmonary artery (*right*) has bypassed the capillaries and entered the interlobular veins (*left*) through the arterio-venous shunt. Magnification about 150 ×.

Fig. 8. The same lung as in Fig. 7 showing the route of injected india ink from the pulmonary artery through the bronchial artery to the submucosal bronchial venous plexus. Magnification about 150 ×.

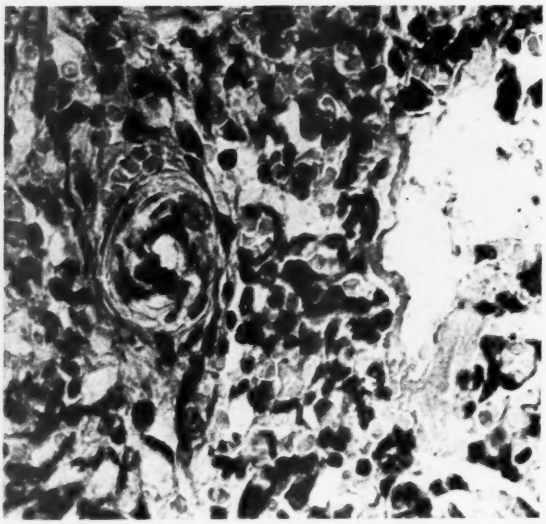

Fig. 9. Congested lung with hyaline membranes. The narrow lumen of the artery, thick muscularis and distended periarterial lymph space filled with blood corpuscles indicates a contracted artery. Magnification about 300 ×.

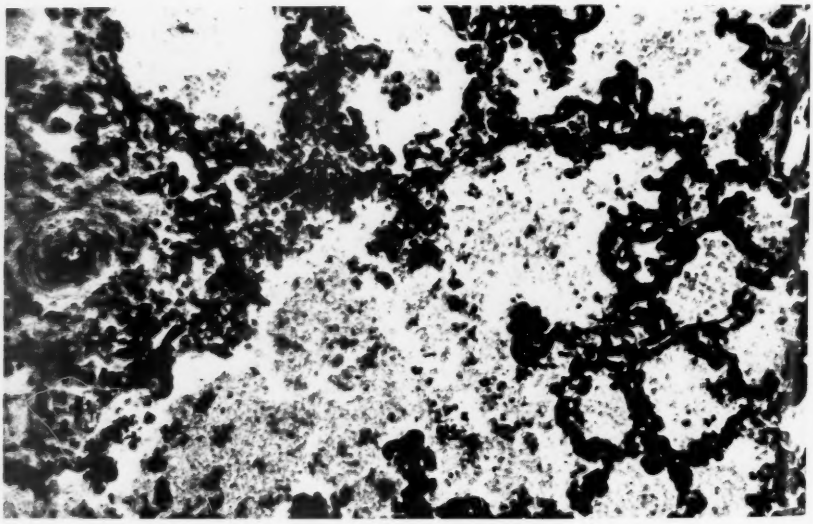

Fig. 10. Prenatal erectile expansion. India ink has been injected into the pulmonary artery (*left*) and the dye has entered the capillary bed, indicating a patent capillary circulation intra vitam. Air spaces filled with abundant blood corpuscles and aspirated matter. Magnification about 150 ×.

The circulatory status in expanded stillborn and neonatal lungs

The microscopic structure of asphyxiated lungs has been described by, among others, Agnes McGregor. Such a lung is characterized by abundant aspirated matter, congestion and typical flame-like petechial hemorrhages. The strong aspiration of amniotic fluid has led to the condition known as "expansion with liquid".

Injection of dye through the pulmonary artery of the lung reveals canalisation of the small ramifications, which clearly distinguishes it from an atelectatic lung. The capillary network becomes filled and forms a single layer common to adjacent air spaces. The air spaces are filled with aspirated matter and extravasal blood. This type of lung expansion may be termed prenatal erectile expansion. (Fig. 10.)

When lungs of asphyxiated fetuses that have survived delivery are examined, they are seen to show these characteristics. This condition has evidently developed prior to birth but has been maintained through the delivery (Fig. 5, areas *1*).

Discussion

Some observations have been described in the literature which are in accord with the results of the present investigation. For instance, Ahvenainen (1948) observed that aspiration of amniotic fluid and lung expansion took place when he asphyxiated cat fetuses in utero. Likewise, Windle (1939) claimed that thorotrast injected into the amnion of a guinea pig is aspirated into the terminal air spaces only if the fetus is asphyxiated. The observations made in the present investigation suggest that a patent capillary bed is synonymous with capillary erection and lung expansion in vivo. Hence recognition of the causal relationships and the continuity of the above processes makes it possible to arrange the respiratory disorders in the perinatal period according to cause and outcome as shown in Chart 1.

Apparently two processes take place when the cardiopulmonary circulation changes its pattern at birth, and both are directed at establishment of pulmonary flow: the reversal of blood flow through the open ductus arteriosus (Dawes *et al.*, 1953; Adams & Lind, 1957) and the canalisation of the non-patent small ramifications of the pulmonary artery. All pressure measurements that have been made hitherto relate to the main arteries and do not reflect the relationships in the pulmonary capillaries at birth. It seems, however, that the pressure relationships known at present are in accordance with the phenomenon of capillary erection. The increase in blood flow and drop in pulmonary pressure when respiration starts are associated with the canalisation of the small ramifications and opening-up

CHART 1

Explanation of Chart 1.—In undisturbed fetal life (Fig. 2) the pulmonary circulation bypasses the capillary bed and is shunted through the arterio-venous anastomoses.

If asphyxiation occurs prior to delivery, it induces the establishment of capillary circulation which leads to an expanded and aspirated lung structure (Fig. 10) besides remnants of fetal atelectasis. This lung status is seen in cases of intrauterine death.

If, however, the fetus has survived the delivery, it is born with impaired lungs which represent a respiratory handicap. Respiratory distress sets in (Fig. 5). The outcome depends on the relative extents of the described changes. Inflation relates to the picture of Fig. 6 where the fetal atelectatic structure and circulatory relationships have been maintained through delivery, and expansion has been affected by vigorous respiratory efforts by the fetus or artificially. Hyaline membranes are an advanced stage of the inflation that develops after a certain time interval.

Neonatal death is caused by impaired diffusion through the capillaries.

Prematures, owing to underdevelopment, are unable to effect a satisfactory capillary circulation and erection, and hence their lungs are of the inflation type and hyaline membranes may result.

Capillary erection must be considered pathological if it occurs prior to the delivery, but physiological if it occurs post partum.

of the capillary bed. Hence, the high pressure in the pulmonary artery during the fetal period does not effect capillary erection because the capillary bed is unconnected. On the other hand, the demonstrated increased pulmonary flow after birth is directed through the capillaries and erects them.

The other opinion that respiratory movements and entry of air are able to draw blood into the lung capillaries is opposed by the observations presented above. We have the abnormal inflation type of aeration and hyaline membrane disease which both are associated with strong respiratory movements, which, however, are unable to effect the opening of the small arteries. In this connection I wish to refer to views presented at the Symposium on Anoxia of the New-Born Infant held in London in 1953, which indicated that no resuscitation apparatus based on the principle of artificial respiration leads to results that are any more favorable than simple cleaning of the nose and throat of the infant.

I wish to draw attention again to the accompanying Fig. 5. What has been the cause of death? Air has entered the lung over wide areas (marked *3*) and the infant has performed vigorous respiratory movements. Hence the ventilatory function seems to be satisfied. The circulatory function is, however, quite unsatisfactory. In the majority of the lung areas (marked *2* and *3*) the capillary circulation is non-patent, while in the small areas (*1*) where the capillary circulation is connected no gas exchange has been able to take place owing to the presence of aspirated matter. The cause of death may have been the insufficient diffusion due to the closed, fetal type of capillary circulation and aspirated amniotic fluid.

More attention should, in my opinion, be paid to the circulatory relationships and attempts should be made to devise resuscitation procedures that promote capillary expansion. Of course, ventilation is necessary if the infant is apneic, but forceful introduction of air into an atelectatic lung may cause an abnormal expansion of the inflation type.

A few remarks relating to my early experiments may be appropriate. I found it difficult to get injected fluid to enter the capillary bed; this must have been due to the closed state of the terminal ramifications. Much later I realized that the real cause for the non-entry of injected fluid was the phenomenon described in this paper. My earlier assumption that blood corpuscles prevented the entry of dye into the capillaries is only partly true. In view of our present knowledge, the destruction of blood corpuscles by deep-freezing in the earlier experiments was a fortunate procedure in that the state of closure of the entries to the capillary bed was discharged by the same operation. It should perhaps be mentioned that capillary erection is not readily effected in a fresh excised fetal lung when this is attempted by artificial means owing to the persistent closure of the pulmonary arterioles.

Acknowledgements

The specimens were prepared in the laboratory of the Department of Anatomy of the University of Turku. It is a pleasant duty for me to express my thanks to Prof. Esko Näätänen, Head of the Department. I am also indebted to the Emil Aaltonen Foundation and the State Commission of Science for grants in aid.

Summary

The existence of capillary circulation in, and the structural appearance of lungs of fetuses that have died perinatally have been studied. The observations point to the following conclusions:

1. The capillary bed is not patent in the atelectatic areas of fetal lungs.
2. The blood flow can bypass the capillary bed through the short-circuit system described by v. Hayek.
3. A non-patent capillary bed implies that no erection of the capillary network has occurred and may be one cause of atelectasis.
4. An asphyxiated fetal lung is characterized by a patent capillary bed and an expanded structure.
5. The patent capillary bed is synonymous with capillary erection and is the prerequisite of normal expansion of the lung if air is available. If the fetus is in utero, the capillary erection will cause amniotic fluid to enter the potential air spaces.
6. Entrance of air into a lung in which the capillary bed is non-patent will result in an abnormal expansion of the lung.

Erection capillaire et aspect structural des poumons du fœtus et du nouveau-né.

On a étudié la circulation capillaire dans les poumons, ainsi que l'aspect de ceux-ci, chez le fœtus décédé à la naissance. Les observations indiquent les conclusions suivantes :

1° Le résau capillaire n'est pas protégé dans les zônes atelectatiques des poumons fœtaux.

2° Le débit sanguin peut écouler dans le réseau capillaire par le système de court-circuit décrit par v. Hayek.

3° Un réseau capillaire non-protégé signifie qu'une érection du réseau capillaire n'a pas eu lieu et que ceci peut être une cause d'atelectase.

4° Un poumon fœtal asphyxié est caractérisé par un réseau capillaire protégé et une structure étendue.

5° Le réseau capillaire protégé est synonyme à l'érection capillaire et est la réquisition préliminaire d'une expansion normale du pumon s'il y a de l'air disponible. Si le fœtus est dans l'utérus, le liquide amniotique entre dans les espaces aériennes potentilles, et cela sera dû à l'érection capillaire.

6° L'entrée de l'air dans un poumon dans lequel le réseau capillaire est non-protégé aura comme résultat une expansion anormale du poumon.

Kapillarerektion und Struktur fötaler und neonataler Lungen.

Das Vorhandensein eines Kapillarkreislaufes bei Föten und die Lungenstruktur von Föten, die perinatal starben, wurden untersucht. Die gemachten Beobachtungen berechtigen zu folgenden Schlüssen:

1. Das Kapillarbett ist in den atelektatischen Räumen der fötalen Lungen nicht offen.

2. Der Blutstrom kann das Kapillarbett mittels Kurzschlussystem, wie es v. Hayek beschrieb, kleinstellen.

3. Ein nicht-offenes Kapillarbett bedeutet aber, dass keine Erektion des Kapillarnetzes zustandekommt und kann so evtl. eine Ursache von Atelektasis sein.

4. Eine asphyktische fötale Lunge ist durch ein offenes Kapillarbett und weite Struktur gekennzeichnet.

5. Das offene Kapillarbett ist gleich kapillärer Erektion und Voraussetzung für eine normale Expansion der Lunge, sobald Luft verfügbar ist. Ist der Fötus in utero, so wird die kapilläre Erektion die Amnionflüssigkeit veranlassen, die potentiellen Lufträume zu füllen.

6. Lufteintritt in eine Lunge, in der das kapilläre Bett nicht offen ist, wird eine abnormale Ausweitung der Lunge zur Folge haben.

La erección capilar y la estructura de los pulmones fetales y neonatales.

Ha sido objeto de estudio la circulación capilar y la estructura pulmonar de fetos muertos en un estadio perinatal. Las observaciones realizadas inducen a sentar las siguientes conclusiones.

1. El campo capilar no es evidenciable en las areas atelectásicas de los pulmones fetales.

2. La corriente sanguínea puede derivar por los cortocircuitos descritos por von Hayek, sin pasar por el campo capilar.

3. El hecho de que no se evidencie el campo capilar implica la falta de erección de la red capilar, que puede ser una causa de atelectasia.

4. El pulmón fetal asfíctico se caracteriza por la existencia de un campo capilar manifiesto y su aspecto expansivo.

5. El campo capilar manifiesto es sinónimo de la erección capilar, y constituye una condición necesaria para la expansión normal del pulmón en presencia de aire. Si el feto se halla en el útero, la erección capilar provocará el paso de líquido amniótico a los espacios aeríferos potenciales.

6. La penetración de aire en un pulmón cuya red capilar no sea patente provocará la expansión anormal del pulmón.

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From the Pediatric Clinic, Karolinska Sjukhuset, Stockholm

Disseminated Lipogranulomatosis (Farber's Disease)

by ROLF ZETTERSTRÖM

At the congress which was held in 1952 by the American Pediatric Society, Farber described the clinical and pathological-anatomical findings in three children, including two siblings, with a disturbance in lipid metabolism of a type not previously described. The initial symptoms, which were already present at birth or soon thereafter, consisted of hoarse crying, respiratory difficulty, feeding difficulties, and such changes of the periarticular tissues that the diagnosis of rheumatoid arthritis appeared probable. During the ensuing course, continued progression occurred, with the appearance of multiple subcutaneous granulomas, predominantly over joints, skin pigmentations, slight liver enlargement, and destructions within the skeleton. The children died at the ages of 14, 13, and 9 months respectively, with symptoms most closely resembling the picture of a respiratory insufficiency. At autopsy similar changes were demonstrated in all three cases. In several organs such as lungs, pleura, pericardium, liver, spleen, lymph nodes, joint synovium, periarticular tissue and the central nervous system, the normal tissues were partially replaced by "foam" cells in addition to a definite cell infiltration being present. In certain areas, especially in the periarticular tissues, diffuse granuloma development was demonstrated. The changes in the central nervous system were of the same type as in Tay–Sachs' and Niemann–Pick's diseases. Chemical analysis (Uzman) showed increase in the lipid content of the spleen, heart, liver and lungs. The lipoid fraction consisted of 33% carbohydrates, 24% lipids and 43% protein or polypeptides. No more detailed analysis could be given. Farber was of the opinion that in the three affected cases there was present a congenital, probably genetically caused, lipoid metabolism disturbance which was related to Niemann–Pick's disease, although it also differed from this in essential regards. The definition *disseminated lipogranulomatosis* was suggested.

No further cases of this disease have been reported and no extensive clinical study of the disease has been made previously. In this report a case will be described which presents such symptoms that the disease picture appears to be identical to those cases described by Farber.

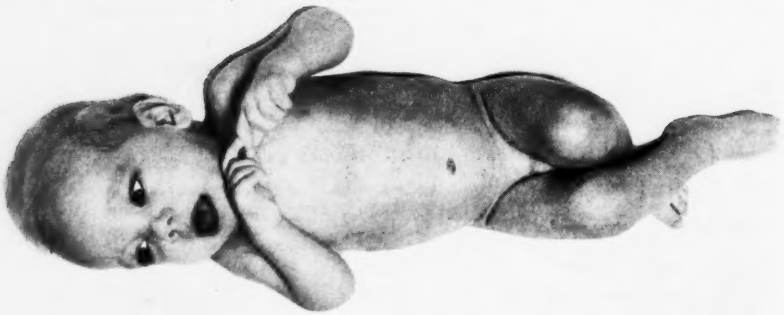

Fig. 1. Patient's appearance at the age of five months. The somewhat puffy face and the open mouth with large tongue are apparent.

Fig. 2. Left hand at the age of five months. The periarticular swellings about the interphalangeal joints are evident. In addition swellings over the wrist and dorsum of the hand. Contractures of the finger joints, especially in the index finger.

Fig. 3. Patient's general appearance at the age of 23 months. Has tracheotomy cannula. He is thin and cachectic with sparse, atrophic musculature and reduced subcutaneous fat. The large, swollen joints with contractures are evident. Numerous subcutaneous granulomas over the spinal processes and thorax are readily seen.

Case Report

J. K., a 4-month-old boy referred to the Pediatric Clinic of Karolinska Sjukhuset for investigation of an illness resembling rheumatoid arthritis.

Second child of healthy, unrelated parents. No known heredity for any special diseases, the other child in the family healthy.

Uncomplicated pregnancy, child born at term, birth-weight 3100 g. During postnatal period intense vomiting of the stenosis type (high-level obstruction). Admitted for this reason to pediatric hospital at the age of 7 days. Nothing indicating an obstruction could be demonstrated, the severity of the vomiting decreased gradually and the boy was discharged at the age of 15 days. Breast feeding initially, but after a few weeks was changed to spoon feeding because of vomiting. Since weight gain was grossly unsatisfactory and the vomiting continued, he was re-admitted to the pediatric hospital at the age of 2½ months. Weight was then only 3600 g. He had at that time a hoarse cry, but otherwise no specific abnormalities. During usual treatment regimen, a successive but somewhat slow increase in weight, weighed 4100 g at 3½ months. No explanation for the persistent hoarseness could be given. At the age of 4 months there

Fig. 4. Left hand at the age of 23 months. Swelling about the joints, the multiple periarticular granulomas and contractures appear prominently.

was a sudden appearance of swelling and redness of the hands, definite swelling about the finger joints, the fingers were held flexed and could be straightened out only with difficulty. The boy clearly had pain in the finger joints. Some days later also slight swelling over the dorsae of the feet and over the knees appeared. The liver which had previously been of normal size was on palpation slightly enlarged and was somewhat firm in consistency.

Examination on admission showed a rather lively 4-month-old boy. Irritable, crying when touched, the cry so hoarse that it was barely audible. Weight 4640 g. Tissues somewhat loose. Normal skin color. Had an unusual, puffy face, appeared to be swollen about the eyes, the mouth was held open, the tongue was somewhat large (Fig. 1). Geographical tongue. Hand joints slightly swollen, fingers in flexion contracture, marked spindle-shaped swelling of the periarticular tissues around the interphalangeal joints (Fig. 2). Slight swelling over the knee joints, moderate flexion contracture. Remaining joints apparently without change. Generalized moderate lymphadenopathy. Liver possibly slightly enlarged. Otherwise no specific abnormalities.

Laboratory examinations.—Hemoglobin 10.9 g%, RBC 3.5 million. WBC 8900, differential count normal. No abnormalities in hemostatics. Urine unremarkable. NPN not elevated. Erythrocyte sedimentation rate 5 mm/hour. WR and serologic reactions for toxoplasmosis negative. Total serum protein 6.5 g%, gamma globulin concentration relatively high for the age, 1.1 g%, but paper electrophoretic examination showed

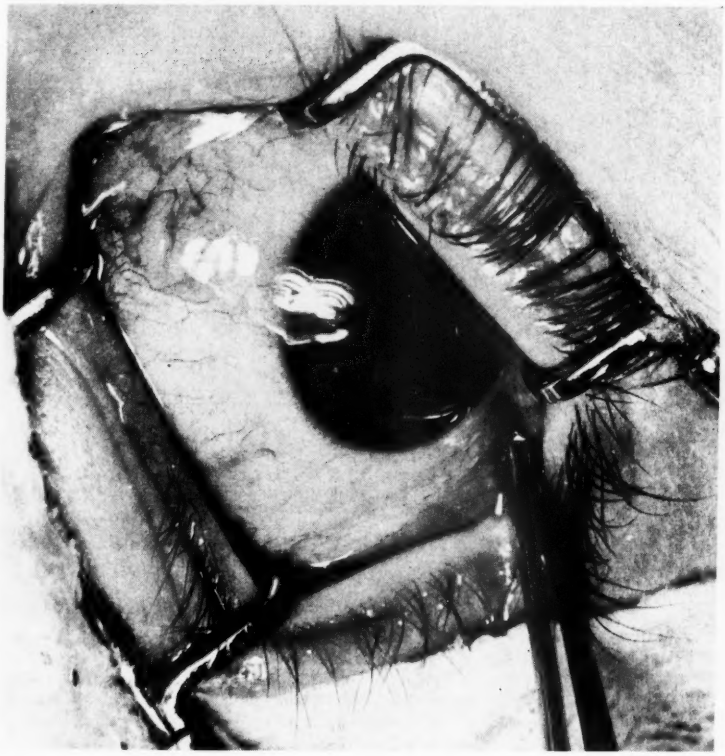

Fig. 5. Left eye at 17 months. The picture shows the xanthoma-like growth of the conjunctiva.

otherwise normal relationships. Thymol moderately high, 8.0 units. Serum electrolytes in normal concentrations. Basal metabolism normal.

Course and treatment.—The patient was cared for during a period of four months. Was afebrile the entire time here. He had numerous large vomitings daily. A slow increase in weight, weighed 5980 g at time of discharge (8 months old). The hoarseness persisted unchanged. Despite treatment with cortisone in high doses (40 mg/day) progression of periarticular joint changes. All joints with the exception of the shoulders slowly became affected with redness and swelling, just as earlier only the periarticular tissue was involved. Pronounced tendency to contractures. The only effect of cortisone treatment was that the pain was thought to decrease.

Re-admitted at the age of 15 months. During the interim continued progression of the periarticular changes, contractures and swelling of all joints,

At the age of 10 months a few subcutaneous granulomas appeared on the scalp and over the ribs. Poor weight gain, increasing hoarseness.

Weight at time of admission 6800 g. Was then generally dystrophic with poorly developed musculature and sparse subcutaneous fat. No pigmentation. Was aphonic,

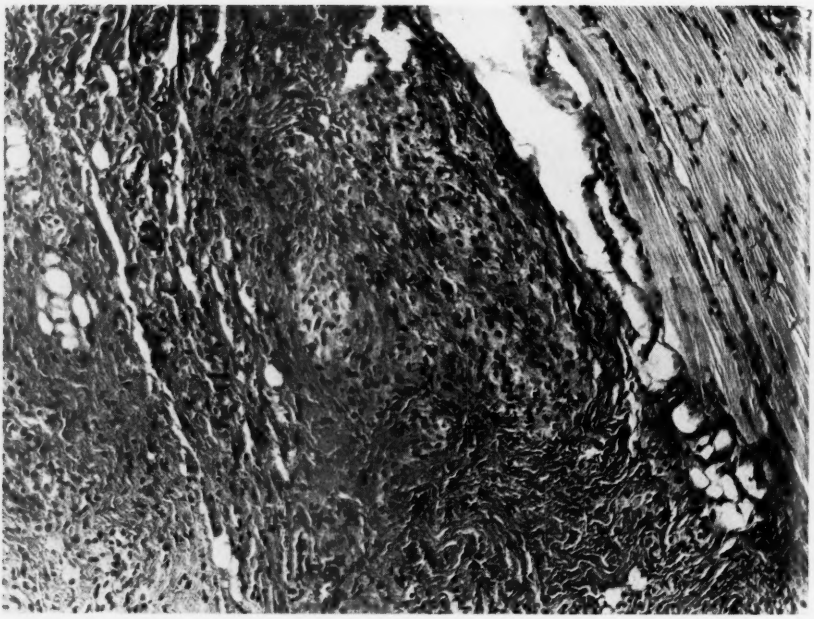

Fig. 6. Microphotograph of section from subcutaneous granuloma over scalp. In the tissue infiltration of moderately large, mostly polygonal, well-demarcated cells with rather small, chromatin-rich nucleus. Rather rich in somewhat granular or foamy cytoplasm. Single large cells but no giant cells. No noteworthy inflammatory reaction. Hematoxylin-eosin.

had significant respiratory difficulty with inspiratory as well as expiratory stridor. Marked thoracic retractions, possibly somewhat emphysematous thorax. In addition to the previously-described periarticular changes there was also seen over both large and small joints numerous bean-sized, subcutaneous, easily movable, moderately firm granulomas. Granulomas were also seen over the back of the head, spinous processes and thorax. The psychic development appeared to be normal for the age. Generalized lymphadenopathy as previously. Impure breath sounds over the lungs. Otherwise no specific abnormalities.

Laryngoscopic examination showed narrowing of the air passages due to granuloma formation. Tracheotomy was carried out as an acute, life-saving procedure.

The boy was cared for at the Clinic for a total of 11 months, to the age of 26 months, when he was transferred to another hospital. Slow progression during the ensuing course. The joint pain had, however, entirely disappeared, and the boy developed a significant ability to move about while sitting. Successive increase in the number of subcutaneous granulomas over the joints as well as in other locations (see Fig. 3 and 4). The boy also developed a xanthoma-like growth about the size of a rice kernel in the conjunctiva over the left eye (Fig. 5) which was excised. Retention of the tracheal cannula was necessary the entire time. On many occasions he acquired acute bronchopneumonias which, however, regressed after the usual treatment. Continued tendency to vomiting and poor weight gain, weight at discharge 8100 g.

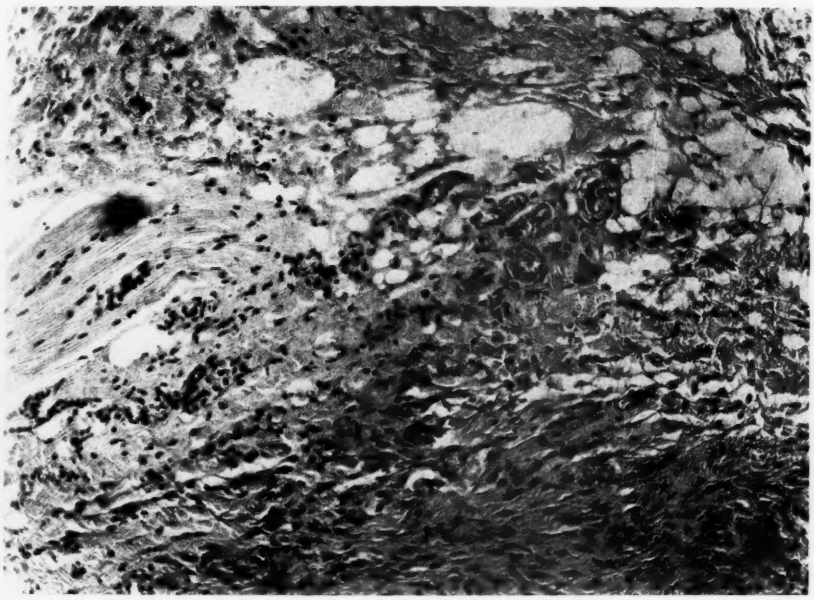

Fig. 7. Microphotograph from another subcutaneous granuloma (over thorax). The histological picture is identical with that in Fig. 6. Hematoxylin-eosin.

Since the stools were rather voluminous despite small food intake, a malabsorption syndrome appears possible. With the exception of a certain steatorrhea (fat absorption coefficient 72%), there are no other signs of deficient absorption.

Further special examinations.—X-ray examinations of the joints have shown only periarticular changes as previously. Reduced mineralization of the skeleton, but no bone destruction. The musculature is atrophic with increase in interstitial fat according to the X-rays. Repeated examinations of the lungs showed miliary infiltrations. Heart slightly enlarged. ECG normal.

Ophthalmological examination gave normal findings as previously. Electroencephalographic tracing showed largely normal results.

Microscopic examination of excised subcutaneous granuloma (*B. Ivemark*) shows appearance of markedly sclerotic connective tissue with moderate number of blood vessels. Here and there appear groups of irregularly formed, rather large, light cells with foamy, granular cytoplasm which gives a weak positive reaction with fat stain. No inflammatory cell infiltration worthy of mention. No giant cells or xanthoma picture. No necrosis (Fig. 6 and 7). In the conjunctival granuloma a similar histologic picture was present (Fig. 8).

Chemical analysis of granuloma (*S. Gardell*).—On the basis of the small amount of tissue submitted, only polysaccharide analysis via aminosugar determination could be carried out. Glucosamine content was 0.5 % and galactosamine content 0.25 %. The examination gave no evidence for an increase in polysaccharides.

Chemical analysis of blood and urine.—Total serum lipids 543 mg%. Total serum

Fig. 8. Microphotograph of the conjunctival granuloma (cf. Fig. 5). Diffuse extracellular fat infiltration with rather abundant number of xanthoma cells. Hematoxylin-eosin.

cholesterol 195 mg%, of which 108 mg% esterified. Serum uric acid content 3.3 mg%. In the urine, according to the chromatographic examination, slight increase in amino acid content, but normal partition. Alpha-amino nitrogen excretion 17 mg/day. Creatine excretion in urine not elevated (2.0 mg/day).

Hematological examinations.—Slight normochromic anemia (hemoglobin 9.5–10.5 g%) but otherwise no noteworthy changes. No abnormal cytological findings in the bone marrow.

Discussion

The described case presents signs of a generalized disease which primarily manifests itself by periarticular changes and formation of granulomas of the so-called lipoid type. It is probable that the early appearance of hoarseness depended on formation of granulomas in the larynx. The earliest type

of periarticular reaction appears to point to a more diffuse initial manifestation in that tissue, but later granulomas developed there also. In addition it is impossible to determine to what degree the various organs are affected. Subcutaneous connective tissue, especially the periarticular, is affected most pronouncedly as well as the subserosal tissue in the larynx. The miliary infiltrations in the lungs point to involvement of that tissue also. Further organs possibly affected are heart (enlargement), liver (transient enlargement) and gastro-intestinal tract (high-grade tendency to vomiting and steatorrhea). To judge from the X-ray examinations, the skeleton appears to be unaffected, and there is likewise no evidence for involvement of the central nervous system. Kidney function appears to be normal.

The course appears to be more benign than in the cases described by Farber, but the prognosis must be regarded as poor. An attempt at treatment with cortisone was unsuccessful.

The examinations which were carried out have given no information as to the etiology and pathogenesis of the disease. No definite metabolic derangements typical for this disease condition could be demonstrated in vivo. However, nothing speaks against Farber's hypothesis that the disease is caused by a disturbance in lipid metabolism.

Certain analogies are found with Hand–Schüller–Christian disease, which has also been pointed out by Farber. The results of the histological examinations, however, are more in agreement with the theory of a primary lipoid metabolic defect rather than that the lipoids should be secondarily gathered in a granulomatous tissue which is primarily the result of the collection of special cell elements. No clinical similarity between the described case and Niemann–Pick's disease is found (cf. Thannhauser) since the central nervous system is completely intact. It is to be expected, however, that the symptomatology in a disease of the above-described type could vary significantly according to which organ system is affected.

Summary

The clinical picture in disseminated lipogranulomatosis, a disturbance in lipid metabolism described by Farber in 1952, is reported on the basis of the findings in a boy with the clinical signs of that disease. The symptoms appeared immediately after birth. The primary signs of disease were vomiting, hoarseness and later laryngeal obstruction on the basis of granuloma development. Periarticular changes, with swelling over the joints and tendency to contractures as a result, were also early symptoms. Later multiple subcutaneous granulomas appeared which histologically consisted partly of so-called foam cells. The disease has had a slow but progressive course. Attempt at treatment has given no result.

Lipogranulomatose disséminée.

Le tableau clinique de la lipogranulomatose disséminée, un déséquilibre dans le métabolisme lipoïde décrit par Farber en 1952, est expliqué en se basant sur les résultats constatés chez un garçon avec les manifestations cliniques de cette maladie. Les symptômes apparaissent aussitôt après la naissance. Les premiers signes de la maladie étaient: vomissement, enrouement et plus tard obstruction du larynx après développement d'un granulome. Des modifications périarticulaires avec inflammations articulaires, et, comme résultat, tendance aux contractures, furent aussi parmi les premiers symptômes. Par la suite, de multiples granulomes souscutanés apparurent qui consistaient histologiquement en partie de soi-disantes cellules écumeuses. La maladie a eu une évolution lente, mais progressive. Le traitement n'a donné aucun résultat.

Disseminierte Lipogranulomatose.

Das klinische Bild einer disseminierten Lipogranulomatose, einer Störung im Fettstoffwechsel, wie sie Farber 1952 beschrieb, wurde abgehandelt im Rahmen der Beschreibung eines Jungen, der an dieser Krankheit litt: die Symptome traten unmittelbar im Anschluss an die Geburt auf. Die primären Anzeichen dieser Erkrankung sind: Erbrechen, Heiserkeit und später Larynxobstruktion im Rahmen der Entwicklung des Granuloms. Periartikuläre Veränderungen mit Gelenkschwellung und als Resultat die Tendenz zu Kontraktionen, sind ebenfalls Frühsymptome. Später treten multiple, subkutane Granulome in Erscheinung, deren histologische Struktur teilweise sogenannte „Schaumzellen" aufweist. Die Erkrankung hatte eine langsame, aber progressive Verlaufsform. Ein Behandlungsversuch hatte keinen Erfolg.

Lipogranulomatosis diseminada.

Se describe el cuadro clínico de la lipogranulomatosis diseminada, transtorno del metabolismo de los lipoides descrito por Farber en 1952, basándose en el caso de un niño con manifestaciones clínicas de esta enfermedad. Los síntomas aparecieron inmediatamente después del nacimiento Las primeras manifestaciones morbosas fueron vómitos, ronquera y, más tarde, obstrucción laríngea por la proliferación granulomatosa. Entre los síntomas precoces existian también alteraciones periarticulares, con tumefacciones en las articulaciones y tendencia a las contracturas. Ulteriormente aparecieron múltiples granulomas subcutáneos constituidos histologicamente por las denominadas células espumosas La enfermedad ha presentado un curso lento pero progresivo. Las tentativas terapéuticas no han dado resultados.

Acta Pæd. Zetterström

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The Fibrinolytic Activity in the Newborn

by GUNILLA BERGLUND

The blood clot formed *in vivo* is liquified through fibrinolysis. This is as a rule a local process, where the fibrinolytic activity is formed under the influence of an activator, liberated from the injured tissue. Sometimes the fibrinolysis can be a generalized process. This happens when the proactivator in the blood changes to an activator (Astrup & Permin), and a hemorrhagic disorder may arise. This was first observed in connection with some surgical procedures. Biggs, Macfarlane & Pilling later showed that stress, as well as injections of adrenalin, could generate fibrinolysis. The amniotic fluid has a strong fibrinolytic activity. Albrechtsen, Storm & Trolle have described a case of fibrinolysis in a mother at delivery, where the fibrinolysis was due to infusion of amniotic fluid. Recently Astrup has reviewed fibrinolysis in the organism. Ströder & Künzer have found in their studies on the coagulation process in children, that there is a higher fibrinolytic activity in the cord blood than in the blood of adults. In order to investigate if the fibrinolytic activity could be one of the causes of neonatal bleeding disorders, the fibrinolytic activity of normal newborns has been investigated.

Material

In 143 cases the fibrinolytic activity has been investigated in the cord blood. Only full-term infants have been studied, where the delivery has been normal, the mother has been healthy and the condition of the child during the first days of life seemed entirely normal.

In 78 cases infants have been investigated during their first days of life. Only in a few cases has more than one investigation been made in the same child during the newborn period. Also this group consists of apparently healthy infants.

In 9 cases the mothers have been investigated immediately after delivery.

Method

The blood was drawn by sterile puncture. Sodium citrate was used to prevent clotting. Samples from infants which have been taken after ligation of the umbilical cord have been drawn from the internal jugular vein where the specimen is not contaminated with tissue fluid. In the mothers the puncture was performed in the cubital vein. Special

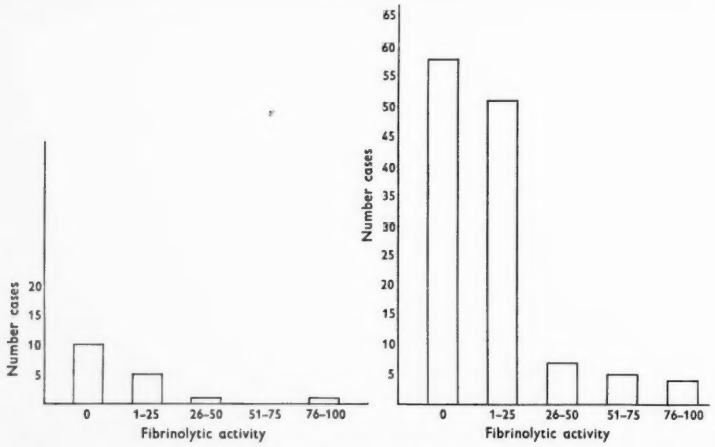

Fig. 1. Fibrinolytic activity in the umbilical cord blood. Left: Blood examined within 1 hour after the sample was taken. Right: Blood examined after storage in refrigerator.

care was taken to let the puncture go easily and to obtain blood at the first puncture, this to avoid the activating effect of tissue fluid.

Plasma was used for the investigations. When the cord blood was examined, it was difficult to examine this immediately after the sample was taken. This material was divided into 2 groups: a smaller group where the blood was examined within 1 hour after the sample was taken, and a larger group, where the blood was put into a refrigerator at + 4°C during a time varying up to 12 hours before the examination, after which time the plasma was separated and then frozen until the investigation was performed (Fig. 1). No significant difference was obtained between these groups. Blood obtained from the venous punctures was examined immediately, that is, within 1 hour following separation of the plasma.

The fibrinolytic activity was examined with the fibrin plate method described by Astrup & Müllertz. Bovine fibrinogen was used with a fibrinogenic concentration of 0.15%, pH 7.8, and the ionic strength 0.15. Nine ml of the fibrinogen solution was clotted in a Petri dish with 20 NIH units of thrombin. Exactly 0.03 ml of the actual plasma was placed as a drop on the plate. Afterwards it was incubated for 18 hours at 37°C prior to reading. On the digested zone around the drop the product of 2 perpendicular diameters was calculated. Every sample of plasma was examined on 2 or 3 plates and the mean value used. As a standard, 0.01 mg trypsin was used, where the diameter was 10 mm and the comparison number thus 100.

Results

In about half of the cases where the umbilical cord blood was examined, no fibrinolytic activity could be demonstrated with this method (Fig. 1). In the other cases the main part shows a mild activity, but there are also cases which have a moderate fibrinolytic activity.

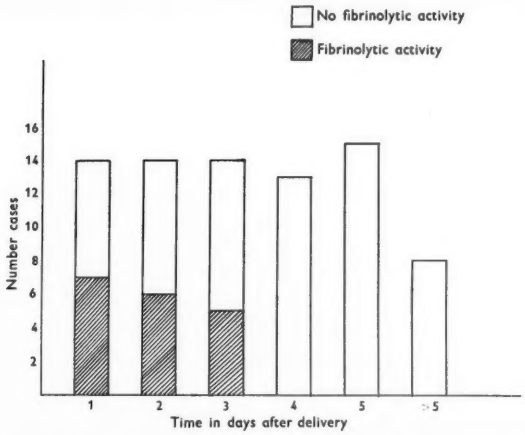

Fig. 2. Fibrinolytic activity in the blood during the first week of life.

The investigations show that the fibrinolytic activity decreases during the first days of life (Fig. 2). In one-day-old children there is still a fibrinolytic activity in almost half of the cases. In all these the activity was mild, that is, below 25. With advancing age the fibrinolytic activity decreases and after the third day of life no activity has been demonstrated.

When the fibrinolytic activity in the blood of the mother is compared with that in her child's cord blood, no correlation is obtained, as seen below.

Mother	9	0	0	100	0	16	24	12	0
Child	0	100	9	8	0	16	0	0	0

Discussion

In his material of adults Truelove points out the lability of the fibrinolytic activity. In his investigations the lability decreases quickly after the first 15 minutes, later the reduction is slower. In my material the fibrinolytic activity has not been investigated within 15 minutes, so that the possibility that a higher activity may exist cannot be excluded. In the present material no significative difference has been demonstrated between the power of fibrinolytic activity of the cord blood investigated within 1 hour and that kept in the refrigerator. Of course this does not prove that a reduction of the fibrinolytic activity during the interval up to 12 hours has not taken place, but the result indicates that, from the practical point of view, also samples taken with a certain delay are fit for use.

The etiology of the fibrinolytic activity remains obscure. As the fibrinolytic activity decreases within a few days after delivery one may suppose

that there are circumstances at the delivery responsible for its release. Partly this could be due to the stress on the infant of an apparently normal delivery. The hypoxemia of short duration during the final stage, even in those cases where there are no clinical signs of asphyxia, could be one cause. In certain cases the child may get an infusion of the fibrinolytically active amniotic fluid. There is no evidence supporting the view that the fibrinolytic activity can be passively transported from mother to child. Investigations performed both in mother and in child demonstrate that there is no correlation between the values of their fibrinolytic activity.

Summary

The fibrinolytic activity of umbilical cord blood was investigated in 143 cases. In about half of the cases no fibrinolytic activity could be demonstrated. In the other cases there was a mild or moderate fibrinolytic activity. There was no difference in activity between the samples investigated immediately after the puncture and those kept in refrigerator up to 12 hours.

The course of the fibrinolytic activity has been followed in infants during their first week of life. The number of cases with proved fibrinolytic activity decreases successively, and it is not possible to show any fibrinolytic activity after the third day of life.

In an investigation of the fibrinolytic activity in mother and child in 9 cases it has been demonstrated that there is no correlation between their fibrinolytic activities. From this it may be concluded that there is no evidence indicating that fibrinolytic activity is passively transferred from mother to child. Obviously it arises in the fetus. Various possibilities of its origin have been discussed.

L'activité fibrinolytique chez le noveau-né.

L'activité fibrinolytique du sang du cordon ombilical était examinée dans 143 cas. Dans environ la moitié des cas on n'a pas pu démontrer d'activité fibrinolytique. Il n'y eut pas de différence en activité entre les échantillons examinés immédiatement après la ponction et ceux conservés dans le réfrigérateur pendant 12 heures au maximum. Le cours de l'activité fibrinolytique a été suivi chez les nourrissons durant la première semaine de leur vie. Le nombre de cas avec une activité fibrinolytique prouvée diminua successivement et il n'est pas possible de démontrer quelque activité semblable après le troisième jour de vie. Selon une recherche de l'activité chez la mère et l'enfant, 9 cas ont démontré qu'il n'existe pas de corrélation entre leurs activités. Il est à conclure de ce qui précède qu'il n'y a pas de preuve indiquant qu'une activité fibrinolytique soit transférée d'une façon passive de la mère à l'enfant. Il est évident qu'elle se produise chez le fœtus. Plusieurs possibilités concernant son origine ont été discutées.

Fibrinolytische Aktivität beim Neugeborenen.

Die fibrinolytische Aktivität des Nabelschnurblutes wurde in 143 Fällen untersucht. In etwa der Hälfte aller Fälle konnte keine fibrinolytische Aktivität aufgezeigt werden. In den übrigen Fällen war diese gering oder nur mässig. Es bestand hinsichtlich der gen. Aktivität kein Unterschied zwischen Proben, die direkt nach der Punk-

tion untersucht wurden und solchen, die erst nach 12 Stunden — im Kühlschrank aufbewahrt — zur Untersuchung kamen. Der Verlauf der fibrinolytischen Aktivität wurde bei den Kindern (Säuglingen) während der ersten Lebenswoche verfolgt. Die Zahl der Fälle mit erwiesener fibrinolytischer Aktivität ging langsam zurück und es ist unmöglich, eine derartige Aktivität nach dem 3. Lebenstage aufzuzeigen. Anlässlich einer Untersuchung der Aktivität in 9 Fällen bei Mutter und Kind konnte gezeigt werden, dass betr. beider Aktivitäten keine Beziehung untereinander besteht. Es kann daraus gefolgert werden, dass kein Anlass und Beweis vorliegt anzunehmen, dass die genannte fibrinolytische Aktivität passiv von der Mutter auf das Kind übertragen wird. Offensichtlich entsteht diese im Fötus. Verschiedene Möglichkeiten ihrer Entstehung werden diskutiert.

La actividad fibrinolítica en el recién nacido.

Fué objeto de investigación la actividad fibrinolítica de la sangre del cordón umbilical en 143 casos. En casi la mitad de los casos no pudo demostrarse actividad fibrinolítica alguna. En los restantes casos, existía discreta o moderada actividad fibrinolítica. No se observaron diferencias entre la actividad de los especímenes estudiados inmediatamente después de la punción y los mantenidos en la nevera durante más de 12 horas. Se siguió la evolución de la actividad fibrinolítica en los niños durante la primera semana de la vida. El número de casos con actividad fibrinolítica demostrada disminuye progresivamente y no es posible evidenciar tal actividad después del tercer día de vida. En 9 casos, la investigación de la actividad tanto en la madre como en el niño ha demostrado que no existe correlación alguna entre sus valores. De ello cabe inferir que no existe ninguna evidencia que indique que la actividad fibrinolítica sea transmitida pasivamente de madre a hijo. Se origina por tanto en el feto. Se discuten diversas posibilidades de este origen.

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A New Method for the Measurement of the Partial Pressure of Blood Gases and of the Principal Data of Ventilation

Results of Measurements Made in Normal Children and in Children under Respirator Treatment for Respiratory Paralysis

by D. BODA and L. MURÁNYI

In the appraisal of respiratory disturbances the most important evidence would be the knowledge of the partial carbon dioxide and oxygen tension (P_{CO_2} and P_{O_2}). Unfortunately, the determination of blood gas tension is a very difficult procedure. The direct techniques (14), including also the much-liked Riley and Schollander method (12) require most meticulous and involved work. Although somewhat simpler, the indirect methods (1, 10) also require great experience in technique and costly equipment. In any of these procedures blood should be obtained by arterial puncture.

Our method is based on the observation that, as a result of diffusion through the gastric mucosa, an equilibrium will develop between the gases introduced into the stomach and the blood gases. A modified Miller–Abbot tube is inserted into the stomach and in the inflated, thin-walled balloon attached to it the air will soon become identical in composition with the blood gases, as far as tension is concerned.

The observations concerning diffusion through the gastric mucosa date back to almost a century ago. In his work on the subject published some 50 years ago Ylppö (16) referred to reports published decades earlier. Ylppö was concerned with the possibility of introducing oxygen. Proceeding along these lines he developed the method of introducing oxygen intragastrically, a procedure still employed in the treatment of asphyxia of newborn and premature infants.

Another group of workers (3, 6, 9) investigated the problem from the point of view of the pathomechanism of paralytic ileus. It had been recognized by all of them that the air, or some other gas introduced from the outside into the different sections of the intestine, would become closely

similar in gas tension to blood gases. We have made use of this law in diagnosis.

If we know the intragastric P_{CO_2} (which, as it will be seen later, is closely comparable for the P_{CO_2} of arterial blood) it will be obvious that by measuring the other characteristics of CO_2 metabolism it is possible to investigate also the other data of ventilation. If we determine namely simultaneously the CO_2 content of expired air, the CO_2 output per minute and the respiratory frequency, then the minute ventilation, alveolar ventilation, tidal volume, dead space and the respiratory equivalent can be determined by computions.

In this report we discuss the methods employed in our studies, as well as the results obtained in children of different ages, normal and treated in the iron lung for respiratory paralysis.

Methods

A. *Laboratory procedures*

P_{CO_2} in blood was determined indirectly, on the basis of the Henderson–Hasselbach formula, by determining blood pH and total CO_2 in plasma. The plasma pH was determined photometrically, by the method of Van Slyke *et al.* (15). The error of measurement was ± 0.010 pH. Total CO_2 in plasma was determined in the Van Slyke manometric apparatus (16), with the limits of error ± 0.51 vol per cent. The Haldane apparatus was used for the determination of CO_2 and O_2 in gases. The CO_2 in expired air, as well as the CO_2 determination required in the measurement of CO_2 output were carried out by the following titrimetric procedure.

Depending on the expected CO_2 content 20, 40, 100 or 200 ml of air was bubbled through 5 ml of a 0.1 *N* $Ba(OH)_2$ solution from a calibrated syringe with paraffinized piston. The amount of CO_2 absorbed was obtained after titration with 0.1 *N* oxalic acid in the presence of phenolphthalein indicator, by subtraction from the blank value. Constancy of temperature of the air in the syringe was secured by means of a water bath. The CO_2 in the volume of air tested: 0.1 *N* $Ba(OH)_2$ consumed × factor of $Ba(OH)_2$ × factor of syringe × 1.1205.

$$CO_2\% = \frac{CO_2 \text{ content in ml} \times 100}{\text{Volume of air tested, computed for volume at } 0°C}.$$

Even with smaller test volumes the analytical error of the method does not exceed 0.1 vol per cent. When determining from 200 ml of air the accuracy of the method was superior to that of the Haldane method.

B. *Techniques*

Blood was taken by an air-tight technique with heparinized glass syringes. Until tested the blood was stored for a short time under paraffin oil on ice.

Arterialized blood was taken after 20 minutes in a 45°C water bath from a hand bath.

The gastric tube used was similar to the Miller–Abbot tube. The lemon-shaped balloon was attached to the tube as with the original Miller–Abbot tube. Our balloon

was 50 ml in capacity and was made of 0.05 mm thick, twice-dipped rubber. The tube itself was thinner than the Miller–Abbot tube and had a single lumen. It was introduced through the nose in every case and was fixed to the skin near the nose by a silk thread held in place by elastic tape. After the tube had been introduced into the stomach 50 ml of a gas mixture was usually administered. When the P_{O_2} was also to be determined, 7 per cent O_2 and 93 per cent N_2 was the gas mixture employed. Otherwise, atmospheric air was used. Three hours later a syringe with paraffinized piston was attached to the tube, 10 ml gas mixture was aspirated to fill the dead space of the tube and syringe, and the gas to be tested was only drawn up after that. The results here presented are fasting ones obtained in the morning. When an indwelling tube was used, or when the test was made during the day, it was carried out 4 hours after the last meal.

The mixed, expired air was collected directly from the pharynx of the patient, by means of a rubber tube of small diameter. Depending on age, the tube was inserted to a depth of 3 to 4 cm through the nose and was fixed in place. After the patient had become quiet, the test air was sucked into a syringe in small single volumes invariably during expiration, visually checking the motions of the chest. After some practice a difference in the results of two parallel tests not exceeding 0.3 vol per cent can be achieved.

The determination of CO_2 production is carried out essentially by the open-system metabolic test method. The equipment required is composed of (1) a nylon tent, (2) a gasmeter, (3) a compensating air-tight dish, (4) a suction motor. The patient is in a transparent nylon sac, having a rigid part at the head piece, but otherwise it adheres to the neck air-tight. Two rubber tubes extend from the sack. When the test subject is in the iron lung, the same tent is used so that the head of the patient is in the rigid head piece and the neck piece secures hermetic sealing. The respirator thus cannot suck air out of the tent. During the test the rubber tube extending from the tent is connected to the gasmeter and air container, and through these, with the suction motor.

The other tube provides for the replacement of sucked-out air. The suction motor has a delivery of up to 6 times the expected minute ventilation. Thus, during the tests there is a negative pressure of about 1 to 2 cm of water within the tent and the CO_2 concentration is below 1 per cent. Besides the data for temperature and barometric conditions we must know the exact delivery of the motor, as well as the CO_2 content of the compensating dish. Owing to the small dead space in the system, the value of the latter already becomes constant during the first few minutes of testing. In this series we relied upon the values obtained 10 and 15 minutes following the start of experiment.

Formulae and signs

P = gas tension in mm Hg.
P_B = barometric pressure in mm Hg.
P_{H_2O} = water vapor tension in mm Hg.
F = fractional concentration in dry gas phase.
$F_{I_{CO_2}}$, $F_{V_{CO_2}}$, $F_{E_{CO_2}}$, and $F_{G_{CO_2}}$ = CO_2 concentration in atmospheric air, in the compensating dish, in expired air and in gastric air, respectively, expressed in ml/100.
STPD = dry gas 0°C temperature, at 760 mm Hg pressure.
BTPS = gas saturated with water vapor of 37°C, at 760 mm Hg pressure

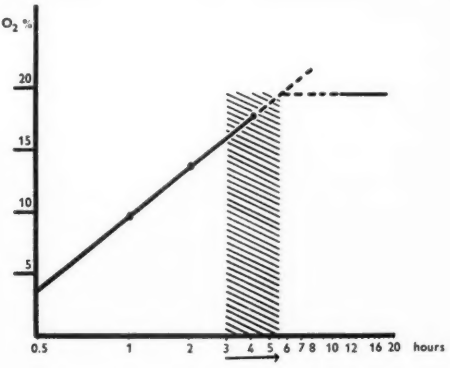

Fig. 1. Gas diffusion through the wall of the rubber balloon, in model experiment. At 0 minute the balloon filled with N_2 is submerged in atmospheric air saturated with water vapor of 37°C. x-axis: time. Logarithmic scale. y-axis O_2 per cent.

V_{STPD}, V_{BTPS}, V_{ATPS}, V_T, V_D = gas volume at 0°C, dry, at 760 mm Hg, at 37°C saturated with water vapor, at 760 mm Hg; at a given pressure and temperature, saturated with water vapor; tidal volume (l. BTPS); dead space (l BTPS).

$\dot{V}_E$, $\dot{V}_A$, $\dot{V}_{CO_2}$, $\dot{V}_M$ = expired air ml/min BTPS; alveolar ventilation ml/min BTPS; CO_2 output ml/min STPD; motor delivery ml/min STPD.

$R = \dot{V}_E/\dot{V}_{CO_2}$ = respiratory equivalent.

$$P = F(P_B - P_{H_2O}), \qquad V_T = \dot{V}_E/f$$

$$V_O = V_{AIPB}\frac{P_B - P_{H_2O}}{760} \times \frac{273}{273 + C^\circ}, \qquad V_D = \frac{\dot{V}_E - \dot{V}_A}{f}$$

$$V_{BTPS} = 1.210 \times V_{STDP}, \qquad \text{Resp. equ.} = \dot{V}_E/\dot{V}_{CO_2}$$

$$\dot{V}_{CO_2} = \dot{V}_M \cdot F_{V_{CO_2}}$$

$$\dot{V}_E = \frac{\dot{V}_{CO_2} \times 1.210}{F_{E_{CO_2}}}$$

$$\dot{V}_A = \frac{\dot{V}_{CO_2} \times 1.210}{F_{G_{CO_2}}}$$

Results

1. *Diffusion of gases through the wall of the balloon.*—The rate of gas diffusion through the balloon on the gastric tube had been measured first in model experiments. Fig. 1 shows the O_2 content of the gas in the balloon on the basis of a typical measurement. At onset of the test the balloon had been filled with N_2 and subsequently it was submerged in the common air saturated with water vapor in a sealed flask, which was in a 37°C water bath. When the results are plotted on semilogarithmic paper, a straight line is obtained. A similar line is obtained when filling is with CO_2, except for the well-known fact that the diffusion rate of CO_2 is higher. Fig. 1 illustrates

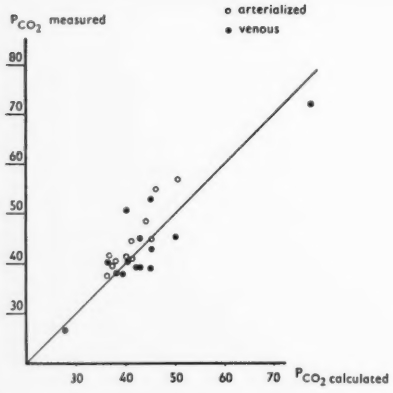

Fig. 2. Correlations between the blood P_{CO_2} (x-axis) computed from the pH and CO_2 concentration and the P_{CO_2} measured in the stomach (y-axis). O, normal arterialized blood; ●, tests on venous blood from patients treated in a tank respirator for respiratory paralysis.

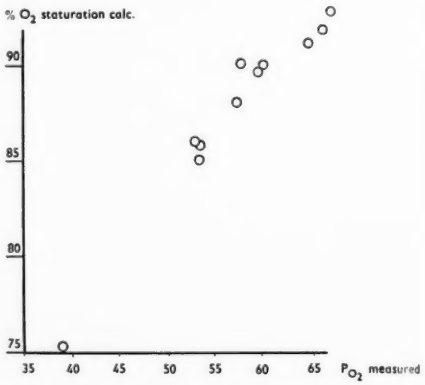

Fig. 3. P_{O_2} measured in the stomach and the O_2 saturation of blood, as determined from the Rahn and Fenn diagram. x-axis: gastric P_{O_2}. y-axis: calculated O_2 saturation of blood.

clearly that even the greatest possible difference in partial tension between the gas in the balloon and the blood gases (3 to 4 vol per cent) will be equalized within 3 hours.

2. *The correlations between the P_{CO_2} computed from plasma pH and plasma CO_2 and the P_{CO_2} measured in the stomach* are illustrated in Fig. 2. The results obtained in tests made on symptom-free patients convalescent from different diseases are designated with O. The blood test for comparison was made in arterialized venous blood, in order to avoid arterial puncture. The measurements designated with a dot were made in patients treated in the respirator for respiratory paralysis. Here pH and CO_2 were determined in venous blood. Fig. 2 reveals that a close correlation exists between the blood P_{CO_2} and the intragastric P_{CO_2} values. This applies particularly to the comparison made with arterialized venous blood. The single deviations are due to the fact that in contrast with the intragastric measurement the determination of the blood P_{CO_2} reflects the conditions prevailing at a given moment only and this can be considerably affected by the circumstances of obtaining the sample, especially in the cases treated in the respirator. It can be also seen in Fig. 2 that the intragastric P_{CO_2} is somewhat higher than the P_{CO_2} of arterialized blood and somewhat lower than that of venous blood. This means that the intragastric P_{CO_2} reflects the state in the arterial branch of the capillaries.

3. *The O_2 saturation measured on the basis of the intragastric P_{CO_2} and the*

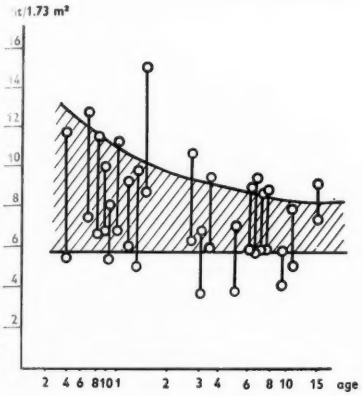

Fig. 4. Minute ventilation and alveolar ventilation (lower point) according to age. x-axis: age in logarithmic scale. y-axis: alveolar and minute ventilation, respectively, in litres, computed for 1.73 square metres of body surface area.

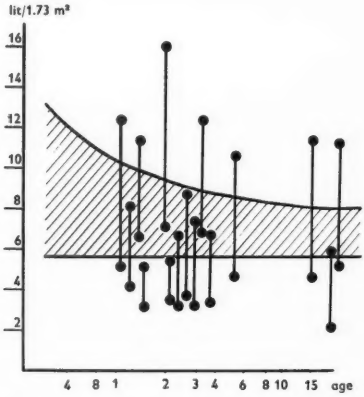

Fig. 5. Minute ventilation and alveolar ventilation in children of different ages, treated in the iron lung for respiratory paralysis. The structure of the figure is the same as that of Fig. 4.

Rahn and Fenn diagram.—We had been unable to compare the intragastric P_{O_2} and the blood P_{O_2} values. In Fig. 3 are presented the intragastric data for 8 normal children. According to the Rahn & Fenn diagram (11) these values are equivalent with the O_2 tension of blood saturated with oxygen at about 75 to 80 per cent, on the basis of the P_{O_2} and the simultaneously measured P_{CO_2} values. Also these few data indicate that the gas tension measured in the stomach is the reflection of the state in the arterial segment of the capillaries.

4. *Minute ventilation and alveolar ventilation values measured in normal children of different ages and computed for 1.73 m² of body surface area.*—Fig. 4 shows these values, grouped according to age and, to facilitate comparison, computed for 1.73 m² of body surface, this being the average body surface value for adults. A line connects the alveolar and the minute ventilation values obtained in the same case. The normal distribution of the difference between the two values is shown by shading. The values for alveolar ventilation, as computed for the same body surface area, are closely comparable at different ages. In contrast to this, the dead space being larger, the minute ventilation is relatively much greater in infants. From this point of view, the basal state of infants is disadvantageous as compared to that of later ages.

5. *Minute ventilation and alveolar ventilation values for patients of different ages, treated in a respirator for respiratory paralysis due to poliomyelitis, as*

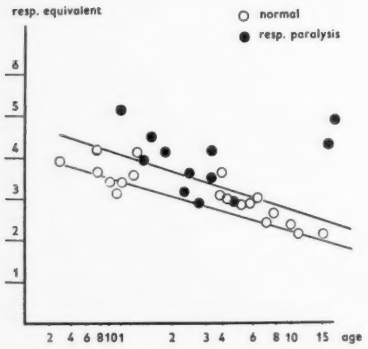

Fig. 6. Respiratory equivalent according to age. x-axis: age, in logarithmic scale. y-axis: respiratory equivalent. ○, normal child; ●, patient treated for respiratory paralysis.

computed for 1.73 m² body surface area.—If we compare the values obtained for the patients treated in the iron lung for respiratory paralysis due to poliomyelitis with the ones obtained for the normal group (Fig. 5 and Fig. 4, respectively) it will be seen that, unlike the normal group alveolar ventilation is highly variable, either due to a diminution in metabolic rate (which was very low in some of our cases), or to hypoventilation. The difference between the alveolar and minute ventilation is considerably increased more than once. As a result of treatment in the respirator, the basal state of ventilation deteriorates progressively. At this time we do not wish to deal with the single cases, with the analysis of the role played by the duration of respirator treatment, the different respiratory complications or the loss of elasticity of lung tissue.

6. *The changes with age in the value of the respiratory equivalent* in normal (○) and poliomyelitic (●) subjects are presented in Fig. 6. The respiratory equivalent decreases with age (8). In general, in cases of respiratory paralysis its value is higher at any age than the normal. Thus, ventilation is less economical in young age, and particularly so in respiratory paralysis.

Discussion

To determine the partial tension of blood gases has long been a desired goal in practical pathophysiology. The analysis of alveolar air was an attempt to achieve this aim. It has been shown that the P_{CO_2} of blood was essentially identical with that of alveolar air. This justifies the use of complicated equipment intended to eliminate the sources of error of the collection of alveolar air. Linderholm collects alveolar air from the area of the carina in patients with respiratory paralysis (7). Although his procedure is good and his results agree satisfactorily with the values for P_{CO_2} in blood,

in the presence of respiratory complications considerable differences may occur (5).

The perspectives of our method are very favourable. It determines with simple equipment, in a bloodless way the most important data for the control of respiratory function, first of all the P_{CO_2} in blood. It is hoped that it will prove itself to be just as good for the measurement of the P_{O_2}, too. It depends only on technical details that the data be shown continuously by a suitable apparatus, independent of whether the test subject is unconscious, an infant, or a premature baby. This is of particular importance in the appraisal of respiratory function, from the point of view of directing treatment in cases of disturbed respiration, primarily in respiratory paralysis, but it may prove to be just as valuable in other fields of medicine as well.

As with clinical methods in general, our procedure also has sources of error. The rubber balloon introduced into the stomach must be of proper quality and the wall thickness must not exceed the optimal to secure adequate diffusion. The balloon must pass the cardia, the sphincter of which should provide for the closed internal milieu. We had no case of aerophagia in our material, but its presence is easy to recognize. Experience has shown us that 3 to 4 hours after the last meal the gas tension can be considered to be constant in the stomach. Apart from these sources of error, our method shows consequent, unidirectional differences as the other standard methods do. For example, the intragastric P_{CO_2}, which reflects the relations in the arterial segment of the capillaries, is higher by about 2 mm Hg than the arterial one. The technique by which we collect the expired air gives a higher CO_2 concentration than that obtained when the measurements are made from a Douglas sac with a controlled valve inserted. For this reason also the computed values of minute ventilation are somewhat lower than the generally known norms. It is difficult to carry out comparative direct spirometric measurements, as it is almost unavoidable that the patient hyperventilate. In spite of the persistent nature of these deviations we have made no corrections. These methods, including those for the determination of the metabolic rate, are known to have considerable limits of error, and deviations within 10 to 15 per cent cannot be taken into consideration. These fundamental statements apply to our method, too. Nevertheless, this does not alter the fact that the observation of the patient complete with data obtained by such measurements give us much better information than the mere clinical appraisal of the conditions in ventilation.

Summary

On grounds of the diffusion through the wall of a thin-walled rubber balloon in the stomach and through the mucosa, the partial pressure of blood gases can be measured quantitatively. From the P_{CO_2} value thus obtained, as well as from the CO_2 concentration of the expired air and the CO_2 output per minute many important data of ventilation can be computed. The procedure does not require the patient's collaboration and thus it can be used equally well in studies on infants and children. By this method we have shown that

(1) the gas tensions measured in the stomach reflect the gas tensions in the arterial section of the capillaries;

(2) normal children of different ages show comparable values for ventilation computed for unit body surface area; in infants the minute ventilation is relatively greater;

(3) in children treated in a tank respirator for respiratory paralysis the ratio of alveolar ventilation to minute ventilation is unfavourable, the respiratory equivalent is high.

Une nouvelle méthode pour la mensuration de la pression partielle du gaz dans le sang et de la donnée principale de la ventilation. Resultats des mensurations faites chez les enfants normaux et chez ceux en traitement respiratoire pour une paralysie de la respiration.

A l'aide d'une diffusion à travers la paroi d'un ballon en caoutchouc mince dans l'estomac et à travers la muqueuse, la pression partielle du gaz dans le sang peut être mesurée quantitativement. De la valeur P_{CO_2} ainsi obtenue, aussi bien de la concentration du CO_2 de l'air expiré et de l'élimination de CO_2 par minute, plusieurs données importantes de ventilation peuvent être calculées. Le procédé ne demande pas la collaboration du malade et, ainsi, il peut être employé aussi bien pour les recherches chez les nourrissons et les enfants. Par cette méthode nous avons démontré que :

1° les tensions du gaz mesurées dans l'estomac reflètent les tensions du gaz dans la section artérielle des capilllaires.

2° des enfants normaux d'âge différent montrent des valeurs comparables pour la ventilation calculée par unité de superficie corporelle; chez les nourrissons, la ventilation par minute est relativement plus élevée.

3° chez les enfants traités dans le poumon d'acier pour paralysie respiratoire, l'indice de ventilation alvéolaire par rapport à la ventilation par minute est défavorable, l'équivalent respiratoire est élevée.

Eine neue Methode der Messung des Partialdruckes der Blutgase und der hauptsächlichsten Daten der Ventilation. Ergebnisse, auf Grund von Messungen, durchgeführt an normalen Kindern sowie an Kindern unter künstlicher Beatmung wegen respiratorischer Paralyse.

Der Partialdruck der Blutgase kann quantitativ gemessen werden auf Grund der Diffusion durch die Wand eines dünnwandigen Gummiballons im Magen und der Diffusion durch die Mucosa. Durch den so erhaltenen P_{CO_2}-Wert, wie auch durch die CO_2-Konzentration der Ausatmungsluft sowie der CO_2-Abatmung pro Minute können viele wichtige Daten der Ventilation errechnet werden. Das Verfahren erfordert keine Mitarbeit des Patienten und kann deshalb ebensogut für Untersuchungen an Säuglingen und Kindern verwendet werden. Bei genanntem Verfahren sahen wir, dass

1. die Gasspannungen, gemessen im Magen, die Gasspannungen im arteriellen Abschnitt der Kapillaren widerspiegeln;

2. normale Kinder verschiedenen Alters vergleichbare Werte für die Ventilation — berechnet nach der Körperoberfläche als Einheit — aufzeigen; bei Säuglingen und Kleinkindern ist die Ventilation pro Minute relativ grösser;

3. bei Kindern, die in Tankrespiratoren wegen respiratorischer Paralyse behandelt werden, das Verhältnis der Alveolarventilation zu Ventilation pro Minute ungünstig ist; das respiratorische Äquivalent ist hoch.

Nuevo método para medir la presión parcial de los gases sanguíneos y los principales datos de la ventilación. Resultados de las determinaciones realizadas en niños normales y niños sometidos a tratamiento por parálisis respiratoria.

La presión parcial de los gases sanguíneos puede medirse cuantitativamente basándose en la difusión a través de la pared de un balón de caucho de paredes delgadas situado en el estómago, y a través de la mucosa. Del valor P_{CO_2} así obtenido, así como de la concentración de CO_2 del aire espirado y el gasto de CO_2 por minuto, pueden calcularse importantes datos ventilatorios. El procedimiento no requiere la colaboración del paciente, por lo que puede emplearse con buenos resultados en lactantes o en niños. Mediante este procedimiento hemos demostrado que:

1. Las tensiones gaseosas determinadas en el estómago reflejan las tensiones gaseosas de la sección arterial de los capilares.

2. Los niños normales de distintas edades poseen valores ventilatorios comparables, calculados por unidad de superficie corporal; en los niños pequeños la ventilación por minuto es relativamente mayor.

3. En los niños tratados en el pulmón de acero por parálisis respiratoria, la relación de la ventilación alveolar y la ventilación por minuto es desfavorable. El equivalente respiratorio se halla aumentado.

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Hyaline Membrane Disease

The Influence of High Oxygen Concentration on Ciliary Activity in the Respiratory Tract. An Experimental Study on Rabbits

by R. BERFENSTAM, T. EDLUND and L. ZETTERGREN

In a review of the literature on the genesis of hyaline membranes in the lungs (Berfenstam *et al.*, 1958) we suggested that the observations made by the quoted authors may favour the theory that the pulmonary lesions in "hyaline membrane disease" in newborn infants could be caused by vascular damage in the lungs. Some of our own experimental observations on oxygen-intoxicated rabbits also indicated that the formation of pulmonary hyaline membranes in these animals could be traced to vascular damage with increased capillary permeability. The exudate was thought to furnish the main part of the material forming the membranes.

However, several authors claim that hyaline membrane disease in newborn infants is caused by aspiration of amniotic fluid and that the membranes are built up by vernix caseosa. Other investigators suggest that the membranes are formed of mucus either aspirated in utero or "endogenous" (for references see Berfenstam *et al.*, 1958).

Since hyaline membranes may be formed by matter retained in the respiratory tract, it seemed worth while to investigate whether oxygen in toxic concentrations diminishes the ciliary movements in the respiratory tract. Such a functional breakdown would probably tend to aggravate membrane formation.

Experimental Procedures

In order to study the ciliary movements we used an *in vitro* method in which the transport of siliconized charcoal by the tracheal epithelium was measured. The tracheal preparations were taken from animals subjected to toxic concentrations of oxygen and from two control groups.

Animals.—Male albino rabbits weighing 2.0 ± 0.1 kg were used. They

were given food and water *ad lib.* during the experiments. The temperature and relative humidity in the stable as well as in the gas chamber mentioned below was kept at 20–23°C, and 70–80 per cent respectively.

The experiments were arranged in the following way.

1. Oxygen-treated animals: The animals were exposed to high concentrations of O_2 during 48 ± 1 hours. The gas chamber previously described (Berfenstam *et al.*, 1958) was used. The oxygen concentration and relative humidity were both 70–80 per cent at atmospheric pressure. The ciliary movements were measured in 100 per cent oxygen.
2. Animals housed in the stable. The ciliary movements were measured in air.
3. Animals housed in the stable. The ciliary movements were measured in 100 per cent oxygen.

Experiments on animals belonging to Groups 1, 2, 3 were performed in random order.

Preparations of the trachea

The animal was killed by a blow on the neck and the trachea was cut out from below the larynx to the bifurcation. The windpipes were immediately placed in airtight perspex tubes containing a cotton pad soaked in Locke's solution[1] and maintained at a temperature of 37°C until the measurements started. The gaseous environments in the perspex tube were the same in which the measurements were made in the different experimental groups.

Performance of the measurements

The tracheal preparations were slit open along the midventral line. The middle third was stretched on a thin cork plate with pins; charcoal was sprayed over the surface.

The plate was then placed in a small, gas-tight perspex chamber. This chamber was held at a temperature of 37°C and the humidity was maintained constant by having a cotton pad soaked in Locke's solution in the chamber. The movements of the particles were observed through a stereo-microscope magnifying 30 times, fitted with a scale in one eyepiece. The time in seconds required for each of 10 particles to travel 10 scale divisions (= 0.5 mm) was measured. Three such measurements were made on each preparation. Between the measurements the charcoal was washed away with warmed Locke's solution and the preparation was sprayed again.

The measurements were performed either in 100 per cent oxygen or in air as stated below.

Preparation of the charcoal used

To five grams of charcoal (Ph.S.Ed. XI) was added 1 drop of Dow Corning Silicone 550 dissolved in 30 ml chloroform. After thorough mixing the solvent was evaporated on a water bath and finally dried at 100°C in a thermostat for 24 hours.

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[1] Locke's solution: NaCl 9.0 g, KCl 0.42 g, $CaCl_2$ 0.18 g, $NaHCO_3$ 0.3 g, Glucose 1 g/litre.

Results

The lungs and the lowest third of the windpipes from 10 animals from each experimental group were studied microscopically (Formaldehyde fixation; Htx–v.Gieson and mucicarmine stained sections). No differences could be found between the three experimental groups.

The other results are given in the tables. It is evident that oxygen exposure for 48 hours disturbs the ciliary transport of charcoal. In 8 animals out of 16 no ciliary transport at all could be observed, in contrast to the findings in the control groups, where transport could be measured in all preparations. The difference is statistically significant ($p<0.01$). [Calculated according to the exact method for 2×2 tables with the use of the binomial theorem.]

Moreover ciliary transport of charcoal in the preparations from the rest of the oxygen-treated animals was observed only in some of the viewing fields. The particles often showed lateral transport. In the control groups the transport was uniform and in all cases directed cranially. Thus the observed qualitative differences in ciliary transport are much greater than is apparent from the transport velocities given in the table. The transport times recorded only show that, in areas where a particle can be transported, the velocities are the same.

No differences could be observed between the two control groups which excludes the possibility that the *in vitro*-exposure of the preparations to pure oxygen causes the above-mentioned effect.

Discussion

In this study the ciliary transport has been observed in that part of the air-way most convenient for such measurements as we performed. It is an open question whether the same functional disturbances take place in the bronchi and bronchioli. Should this be the case, the disturbed or abolished ciliary function in oxygen-poisoned animals would favour the retention in the air-ways of the material forming hyaline membranes, whatever may be the mechanism of their formation.

If the ciliary function in the respiratory tract of newborn prematures responds to high oxygen concentrations in the same way as we have found in rabbits, oxygen therapy ought to be investigated to ensure that the percentages used are not producing ciliary stasis and thereby increasing the tendency to form hyaline membrane.[1]

[1] The theory suggested by Berfenstam *et al.* (1958) that premature infants adapted to the low O_2-tension, occurring in utero, may show symptoms of oxygen poisoning at relatively low O_2-content in their gaseous environment, due to the fact that they are not prepared for extrauterine life, may perhaps stress the necessity to determine a "safe level" for oxygen concentration.

TABLE 1

Observations on ciliary transport.

t = Time in minutes after death of the animals, when the measurements were started; m = arithmetic mean of the time in seconds needed to transport carbon particles 10 scale divisions. For further explanations see text.

	I		II		III	
	t	*m*	*t*	*m*		*m*
	Oxygen-treated animals (48 hours' exposure)					
	Ciliary transport measured in oxygen					
	43	18.3	57	22.22	—[a]	0
	19	6.9	30	16.2	—	0
	47	13.5	69	17.33	—	0
	30	15.9	50	14.66	—	0
	32	3.9	47	8.25	—	0
	50	12.5	60	0	—	0
	23	7.2	31	6.75	41	7.41
	18	0	32	0	—	0
	15	0	22	0	—	0
	19	0	72	0	—	0
	28	0	48	0	—	0
	25	0	51	0	—	0
	29	0	40	0	—	0
	25	0	46	0	—	0
	21	0		0	—	0
	51	0		0	—	0
Mean	29.7	11.20	46.8	14.2		
S. E.	±2.9	±1.99	±3.96	±2.38		
	Animals housed in the stable					
	Ciliary transport measured in air					
	33	6.9	49	6.6	63	7.3
	21	2.4	30	2.5	39	2.2
	32	3.4	40	3.5	47	3.7
	22	6.1	29	5.0	39	5.6
	24	6.1	32	6.3	41	6.2
	28	8.7	37	9.4	47	10.5
	21	6.7	28	8.0	40	11.5
	21	5.6	28	4.5	32	4.7
	21	5.1	28	7.1	39	6.5
	23	14.6	31	12.0	37	14.3
	18	4.3	25	3.9	38	5.0

[a] Time in general not given since several washings with subsequent spraying were performed.

Table 1 (*continued*)

	I		II		III	
	t	*m*	*t*	*m*	*t*	*m*
	21	4.5	26	5.3	35	5.7
	22	7.5	29	10.4	39	12.3
	35	17.8	39	18.5	44	24.0
	29	6.0	36	5.3	44	6.5
	28	14.8	35	14.1	40	17.5
	23	9.0	29	8.3	36	8.5
	23	30.1	31	32.3	40	31.8
	20	27.8	27	28.0	39	39.6
	23	3.7	31	4.0	42	4.6
Mean	24.4	9.6	32.0	9.8	41.1	11.4
S. E.	±1.06	±1.7	±1.30	±1.79	±1.42	±2.21
	Animals housed in the stable					
	Ciliary transport measured in oxygen					
	9	21.3	29	23.9	50	43.7
	7	10.7	20	12.4	35	26.2
	7	3.2	20	4.5	36	3.6
	12	7.9	32	8.0	—[b]	
	12	12.8	40	14.4	60	28.7
	18	32.8	60	33.2	—[b]	
	12	4.3	26	4.7	72	11.9
	29	34.2	40	43.3	73	39.9
	70	11.9	84	10.0	100	9.7
	48	9.6	—[b]		—[b]	
	80	27.2	99	24.8		
	24	3.8	37	12.41	64	6.3
	27	8.3	44	8.6	58	8.8
	31	4.5	44	4.5	56	6.1
	49	4.8	58	10.7	97	7.2
Mean	29.0	13.1	45.2	15.4	61.0	17.4
S. E.	±5.95	±2.74	±6.20	±3.13	±5.46	±4.32

[b] Results omitted owing to technical errors in the thermostat used.

According to several authors (cf. Potter, 1953) deliveries by caesarean section and other complicated deliveries predispose even full-term infants to hyaline membrane disease. We have not been able to find data in the literature which correlate these facts with the premedication given to the mothers before deliveries. Ernst (1938 and 1939) and van Dongen & Leusink (1953) showed that morphine and other opium alkaloids may inhibit ciliary movements in the respiratory tracts of cats. It may be that the premedication and anaesthesia of the mother with, for example, morphine or its derivatives diminishes or stops the ciliary function in the infant. This might likewise increase the risk of retention in the air-ways of material and produce hyaline membrane disease.

Summary

It has been found that in oxygen-treated rabbits, the ciliary transport mechanism, determined *in vitro* using tracheal preparations, is disturbed or lacking before any microscopical changes can be observed in the lungs and air-ways. The results are discussed in relation to oxygen treatment in infants suffering from hyaline membrane disease.

Maladie de la membrane hyaline. Influence de la concentration élévée d'oxygène sur l'activité ciliaire dans le tractus respiratoire. Une étude expérimentale avec des lapins.

On a trouvé qu'en traitant des lapins à l'oxygène, le mécanisme du transport ciliaire déterminé in vitro en employant des préparations trachéales, est troublé ou manque avant que l'on puisse observer quelque changement microscopique dans les poumons et les voies respiratoires. Les résultats sont discutés en rapport avec le traitement à l'oxygène chez les enfants souffrant de la maladie de la membrane hyaline.

Hyaline Membranerkrankung. Der Einfluss hoher Sauerstoffkonzentration auf die Ziliartätigkeit im Respirationstrakt. Eine experimentelle Untersuchung an Ratten.

Man fand, dass bei mit Sauerstoff behandelten Ratten der Ziliartransportmechanismus, *in vitro* an Trachea-Präparaten bestimmt, in Unordnung geriet oder mangelhaft funktionierte, ehe noch irgendwelche mikroskopische Veränderungen in den Lungen und Luftwegen konstatiert werden konnten. Die Ergebnisse wurden diskutiert und in Beziehung gebracht zur Sauerstoffbehandlung bei Kindern mit hyaliner Membran-Erkrankung.

Enfermedad de la membrana hialina. Influencia de una elevada concentración de oxígeno sobre la actividad ciliar de las vías respiratiorias. Estudio experimental en conejos.

Se ha observado que en los conejos tratados con oxígeno, el mecanismo del transporte ciliar, determinado *in vitro* mediante preparaciones traqueales, está alterado o incluso ausente antes de que puedan observarse modificaciones microscópicas en los pulmones o vías respiratorias. Se discuten los resultados en relación con la oxigenoterapia de los niños afectos de la enfermedad de la membrana hialina.

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Etudes spirographiques et oxymétriques chez le nourrisson

III. Epreuve fonctionelle d'hyperventilation chez le nourrisson normal

par F. GEUBELLE

L'hyperventilation volontaire chez l'adulte et le grand enfant constitue une épreuve fonctionnelle et a été utilisée par Van Lingen (10) notamment, chez des malades présentant une cardiopathie congénitale. Elle peut fournir des renseignements très utiles au diagnostic de ces affections.

Au cours d'une étude précédente, nous avons montré que l'ingestion d'un repas liquide peut provoquer, chez le nourrisson, une hyperventilation importante (1).

L'hyperventilation, induite par l'observateur lors de l'administration d'un repas liquide chez le nourrisson, est-elle comparable à l'hyperpnée volontaire de l'adulte et du grand enfant et constitue-t-elle une épreuve fonctionnelle d'hyperventilation? Ou bien : les efforts musculaires requis par la succion, la déglutition et l'hyperpnée elle-même sont-ils si importants que l'ingestion du repas représente une épreuve fonctionnelle d'effort? Pour donner une réponse à cette question, nous avons réalisé chez le nourrisson normal, une série de mesures simultanées de la ventilation, du pourcentage de saturation en oxygène du sang cutané artérialisé, de la consommation d'oxygène, de la production de CO_2 au cours de l'ingestion d'un repas liquide.

Méthodes

Les mesures ont été faites chez 10 nourrissons normaux, âgés de 6 à 28 semaines, chez qui les examens cliniques, radiologiques et de laboratoire, n'ont rien montré d'anormal.

1° La ventilation a été mesurée à l'aide de la méthode pléthysmographique décrite antérieurement et en respectant les conditions de mesure énoncées (2).

2° Le pourcentage de saturation en oxygène du sang cutané artérialisé (p.s.O.) a été mesuré à l'aide d'un oxymètre à lecture directe que nous avons décrit ailleurs (3). La précision des valeurs données par l'oxymètre a été contrôlée au cours d'une série de mesures pratiquées chez l'adulte (4). La concordance entre les résultats lus à l'oxy-

Tableau 1

Les colonnes de 1 à 19 indiquent successivement : 1, l'âge en semaines; 2, le poids en grammes; 3, la taille en cm; 4, le métabolisme standard normal en cal/h; 5, la ventilation normale par minute en ml; 6, la fréquence respiratoire pendant le sommeil (S) et 7, lors de l'ingestion du repas (B); la ventilation/minute mesurée 8, (S) et 9, (B); le volume circulant 10, (S) et 11, (B); l'oxygène consommé/minute 12, (S) et 13, (B); le CO_2 produit/minute 14, (S) et 15, (B); le métabolisme standard mesuré et exprimé en cal/h 16, (S) et 17, (B); le quotient respiratoire 18, (S) et 19, (B). Tous les volumes sont exprimés en ml et corrigés B.T.P.S.

1 âge	2 Poids	3 Taille	4 MS nor.	5 $\dot{V}$ nor.	6 S F	7 B F	8 S $\dot{V}$	9 B $\dot{V}$	10 S V_T	11 B V_T	12 S $\dot{V}_{O_2}$	13 B $\dot{V}_{O_2}$	14 S $\dot{V}_{CO_2}$	15 B $\dot{V}_{CO_2}$	16 S MS	17 B MS	18 S QR	19 B QR
10	4100	58	9,3	800	54	42	1000	1475	18,5	35	36,8	51,3	34,6	47,6	9,8	13,5	0,94	0,93
24	6670	67	14,5	2000	44	49	2225	3650	50,5	74,5	67,8	89,4	59,5	89	17,5	24	0,88	1,0
28	8880	74	18,7	2250	51	55	2360	3750	57,5	68	73,5	81,2	66,7	74	19	21,2	0,91	0,91
22	6650	67	14,5	2000	27	49	1210	2650	45	54	55,4	70,6	54,7	59	14,7	18	1,02	0,83
6	3900	46	7,3	650	32	58	677	1290	21	22.4	28,7	31,2	20,4	29,8	7,2	8,3	0,71	0,95
7	4000	46	7,5	800	30	54	1010	1385	33,7	26,6	31	35	28,8	32,2	8,1	9,3	0,93	0,88
10	4220	46	7,6	900	28	26	907	1140	32,4	44	29,4	32	27	28,5	7,7	8,5	0,92	0,89
8	5400	48	9	1000	29	34	1170	2110	40,7	62	39	45,2	42,9	49,2	10,6	12,7	1,10	1,2
27	7900	72	18	–	36	44	1710	3080	47,5	70	74,5	81	62,5	66,5	19	20,8	0,84	0,82
28	7950	72	18	–	30	48	1590	3210	53	67	75	93,5	68,2	86	19,7	24,5	0,91	0,92

mètre et le p.s.O. du sang artériel, mesuré à l'aide de la méthode de Van Slyke (11), est excellente.

3° L'enregistrement des mouvements de déglutition et de succion a été réalisé à l'aide d'un dispositif simple, imaginé par Hytten (5), que nous avons utilisé au cours de nos recherches antérieures (1).

4° L'oxygène consommé et le CO_2 produit par minute ont été mesurés à l'aide de l'appareil décrit par Noyons (8). La tête de l'enfant est placée sous une boîte en matière transparente (perspex); une pompe aspire l'air contenu dans la caissette. La concentration d'O_2 et CO_2 de l'air recueilli est mesurée simultanément à l'aide de deux analyseurs de gaz : la conductibilité thermique des gaz est différente et influence la résistance d'un fil de platine chauffé électriquement. Cet appareil permet de mesurer d'une façon correcte le « métabolisme standard » dans les conditions décrites par Karlberg (6).

Résultats

Le Tableau 1 donne le détail des résultats obtenus chez les 10 nourrissons. Les valeurs du métabolisme standard considérées comme normales (Colonne 4), ont été calculées d'après le nomogramme de Karlberg (6) en fonction du poids et de la taille. Les valeurs de la ventilation/minute, considérées comme normales, ont été établies d'après les valeurs trouvées dans la littérature (1, 14, 15).

TABLEAU 2

1, Variations du volume respiratoire/minute ($\dot{V}$); 2, de l'oxygène consommé ($\dot{V}_{O_2}$); 3, du métabolisme standard (MS); 4 et 5, de l'équivalent respiratoire (ER); 6, du pourcentage de saturation en oxygène (HbO_2) au cours du sommeil (S); 7, de l'ingestion d'un repas liquide (B), chez le nourrisson normal.

	1 $\dot{V}$ %	2 $\dot{V}_{O_2}$ %	3 MS %	4 S ER	5 B ER	6 S HbO_2 %	7 B HbO_2 %
1	+ 47,5	+ 39	+ 37,8	2,71	2,88	94	94
2	+ 63	+ 31	+ 37,1	3,25	4,09	93	94
3	+ 59	+ 10	+ 11,6	3,21	4,61	94	96
4	+ 120	+ 120	+ 22,4	2,19	3,75	93	94
5	+ 90	+ 8,7	+ 15,3	2,36	4,15	93	95
6	+ 37	+ 18	+ 14,1	3,27	3,97	94	95
7	+ 26	+ 8,5	+ 9,7	3,08	3,57	95	95
8	+ 80	+ 15,7	+ 19,8	3,00	4,67	94	96
9	+ 91	+ 8,8	+ 9,5	2,30	3,80	94	94
10	+ 100	+ 24	+ 24	2,10	3,21	93	94

Le Tableau 2 montre (Colonne 1) la différence entre la valeur de la ventilation/minute (V) pendant le sommeil et pendant le repas, exprimé en % de la valeur obtenue lors du sommeil avant le repas; la différence entre les valeurs du métabolisme standard (Colonne 2) exprimée également en % de la valeur mesurée lors du sommeil avant le repas; l'équivalent respiratoire (ER) : volume respiratoire/minute $\div$ O_2 consommé/minute $\times$ 10 est indiqué dans les Colonnes 3 et 4.

L'examen de ces tableaux montre que lors de l'ingestion du repas :

1° La fréquence respiratoire augmente 8 fois sur 10.

2° Le volume circulant augmente dans tous les cas.

3° La ventilation/minute augmente d'une manière importante (de 26 à 120 % de la valeur obtenue au repos; en moyenne 71,35 %).

4° L'augmentation de la ventilation est plus importante que ne l'est celle du métabolisme standard : l'équivalent respiratoire augmente lors de l'ingestion du repas; à une même quantité d'oxygène consommé correspond une quantité plus grande d'air ventilé.

5° Sept fois sur 10, le pourcentage de saturation en oxygène augmente au cours de l'ingestion du repas.

Discussion

1° Avec le goutte à goutte décrit sur le schéma (Fig. 1), Hytten avait apprécié l'effort réalisé par le jeune nourrisson lors de la succion, en mesurant la

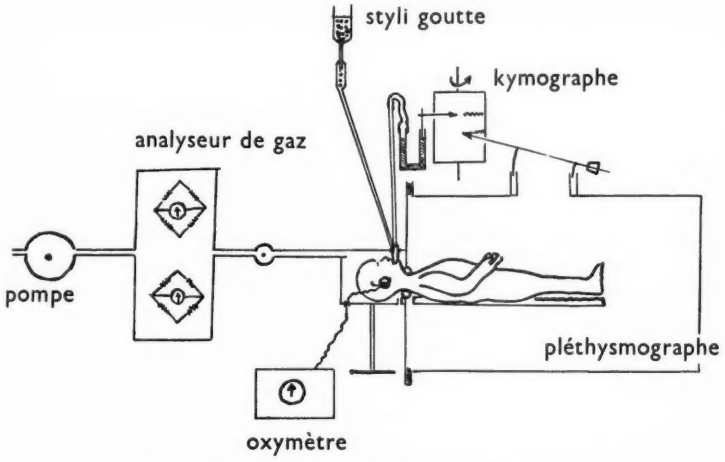

Fig. 1. Schéma de l'appareillage destiné à mesurer simultanément la ventilation, l'oxygénation du sang cutané artérialisé, l'oxygène consommé et le CO_2 produit, au cours de l'ingestion d'un repas liquide chez le nourrisson.

pression négative exercée dans la tétine (5). Avec ce même dispositif simple, dans les mesures effectuées ici, le repas a été administré à un débit tel que tout effort important de succion est évité, dans tous les cas sauf deux (N° 1 et 2).

2° Au cours des épreuves d'effort pratiquées chez l'adulte, la consommation d'oxygène et la ventilation augmentant d'une manière proportionnelle à l'effort fourni. Dans ces cas, l'équivalent respiratoire est peu modifié; chez les athlètes bien entraînés, il peut diminuer légèrement (9).

Au cours d'épreuves similaires pratiquées chez des enfants normaux de 6 à 10 ans, Van Weerde et ses coll. (12) ont trouvé une légère diminution de l'équivalent respiratoire (moyenne au repos; 2,99 : pendant l'effort; 2,74).

Par contre, Wilson et ses coll. (13) ont montré que chez l'adulte normal, au cours de l'épreuve d'hyperventilation spontanée, l'équivalent respiratoire augmente : volume/minute peut être multiplié par 6, tandis que la consommation d'oxygène n'est que doublée.

Les résultats obtenus chez nos 10 nourrissons normaux, montrent que l'hyperventilation provoquée par l'ingestion du repas, dans les conditions énoncées ci-dessus, est comparable à l'hyperventilation spontanée de l'adulte et du grand enfant.

Conclusion

Les épreuves fonctionnelles respiratoires utilisées chez l'adulte, exigent la collaboration du patient et ne peuvent être appliquées au nourrisson. L'in-

gestion du repas liquide, dans les conditions énoncées ci-dessus, constitue la première épreuve fonctionnelle utilisable chez le nourrisson. L'appareillage indispensable est simple : un stilygoutte permet de régler le débit du liquide et un oxymètre donne les valeurs du pourcentage de saturation en oxygène du sang.

L'étude faite chez 10 nourrissons normaux a montré qu'il s'agissait d'une épreuve fonctionnelle d'hyperventilation.

L'étude des modifications de l'oxygénation du sang au cours de cette épreuve fonctionnelle d'hyperventilation chez les cardiopathes congénitaux apportera des précisions utiles pour le diagnostic de ces affections.

Résumé

1° Chez 10 nourrissons normaux, la ventilation/minute, la fréquence respiratoire, l'oxygène consommé et le CO_2 produit, le pourcentage de saturation en oxygène du sang, ont été mesurés pendant le sommeil et lors de l'ingestion d'un repas liquide.

2° L'hyperventilation qui accompagne le repas, est comparable à l'hyperventilation spontanée de l'adulte et du grand enfant.

3° L'ingestion du repas constitue, dans les conditions énoncées, une épreuve fonctionnelle d'hyperventilation utilisable, chez le nourrisson, dans l'étude des fonctions respiratoire et cardio-pulmonaire.

Spirographical and oximetrical studies in infants. III. Functional test of hyperventilation in normal infants.

1. In 10 normal infants, the ventilation/min., the respiratory rate, the oxygen consumed, the CO_2 produced, and the percentage of oxygen saturation of the blood, were measured during sleep and during ingestion of a fluid meal.

2. The hyperventilation accompanying the meal is comparable to the spontaneous hyperventilation of adults and older children.

3. In the above-mentioned conditions, the ingestion of the meal constitutes a functional hyperventilation test which can be used in infants in the study of the respiratory and cardiopulmonary functions.

Spirographische und oxymetrische Studien am Säugling. III. Hyperventilationsprüfung am normalen Säugling.

1. An 10 normalen Säuglingen wurde die Entlüftung/Minute, die Atmungsfrequenz, der Sauerstoffverbrauch, die Kohlensäurebildung und der Sättigungsprozentsatz im Blutsauerstoff während des Schlafes und während der Einnahme der flüssigen Mahlzeit gemessen.

2. Die Hyperventilation, die die Mahlzeit begleitet, ist der spontanen Hyperventilation des Erwachsenen und des grossen Kindes gleichzustellen.

3. Die Einnahme der Mahlzeit bedeute bei den erklärten Bedingungen eine brauchbare Hyperventilationsfunktionsprüfung am Säugling bei dem Studium der respiratorischen und cardio-pulmonairen Funktion.

Estudios espirográficos y oximétricos en el lactante. III. La prueba funcional de hiperventilación en el lactante normal.

1. Se han determinado durante el sueño y después de la ingestión de una comida líquida, la ventilación/minuto, la frecuencia respiratoria, el oxígeno consumido y el CO_2 producido, y el porcentaje de saturación de oxígeno de la sangre en 10 lactantes normales.

2. La hiperventilación que acompaña la ingesta es comparable a la hiperventilación espontánea del adulto y del adolescente.

3. La ingestión de alimento constituye, en las condiciones enunciadas, una prueva funcional de hiperventilación utilizable, en el lactante, para el estudio de las funciones respiratoria y cardiopulmonar.

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Separate Renal Function Studies in Predominantly Unilateral Hydronephrosis[1]

by ROLF ZETTERSTRÖM, NILS OLOF ERICSSON and JAN WINBERG

In a previous communication (Ericsson, Winberg & Zetterström, 1955) the symptoms of renal tubular failure, which may occur early in hydronephrosis secondary to congenital obstruction of the urinary tract, were discussed. The resulting disturbances of electrolyte and acid-base regulation, as well as of renal water reabsorption, have given rise to chronic acidosis or dehydration in some instances. The symptoms of tubular insufficiency which were found to develop before there were signs of any more extensive glomerular damage, as revealed from a normal NPN value, were probably caused mainly by a dysfunction of the distal renal tubules.

In the present study the results obtained from separate tubular function studies of each kidney in two patients with predominantly unilateral hydronephrosis due to ureteropelvic obstruction will be presented. The approximate estimation of the capacity for base and water economy of each kidney suggests that in hydronephrosis there is damage to the distal part of the kidney tubules. Whether this is due to the raised renal intrapelvic pressure or to the chronic pyelonephritis usually present in hydronephrosis remains obscure.

Case Reports

In both patients there was a marked hydronephrosis on one side and a slight hydronephrosis on the other side.

Case 1.—L. B. Born Jan. 24, 1950. A male child, admitted when 5 years old. At the age of 4 months he had a urinary tract infection which probably persisted for some months. Hydronephrosis was diagnosed when the patient was 9 months old. He was without symptoms from the age of one year until four and a half years when he complained of pains in the left side. He had moderate polydipsia, some nausea and vomiting, but no micturition difficulties.

The physical examination on admission did not reveal any abnormalities. The urine was sterile. On intravenous urography there was excretion of a very low concentrated dye by the right kidney, while the excretion of dye by the left kidney was good. On the right side there was a marked hydronephrosis. The left renal pelvis was slightly

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dilated due to an ureteropelvic obstruction. Cystourethroscopy did not reveal any obstruction of the distal parts of the ureters.

Because of pains in the left side an intermittent hydronephrosis was suspected. The left kidney was explored. The pelvis was found to be only slightly dilated and the ureter had a normal width. Adhesions at the ureteropelvic junction were divided. After another two weeks the right kidney was operated upon, and a marked dilatation of the pelvis and ureteropelvic obstruction was found. The renal parenchyma showed no gross damage. A ureteropelvic resection and a pyelostomy were performed. The drain from the right pelvis was left in place for 4 weeks. The postoperative course was uncomplicated.

CASE 2.—J. L. Born Jan. 13, 1954. A male child, admitted when 14 months old. The case history has been reported in a previous article (Ericsson *et al.*, 1955).

Since the age of seven months the patient had periods of fever and abdominal pain. A mass was observed in the right side of the abdomen. On admission the child seemed to be in good condition and had a normal weight. Urine culture positive. Examination revealed an enormous hydronephrosis on the right side due to ureteropelvic obstruction. A moderate hydronephrosis with normal excretion of dye was present on the left side.

A pyelostomy was done because of acute hydronephrosis on the right. Operation for the left hydronephrosis and removal of the right kidney were done later. Histologic investigation of the right kidney *showed signs of chronic pyelonephritis.*

Methods

The function of each kidney was separately estimated during the period when there was a functioning pyelostomy. The urine which was obtained from the pyelostomy gave information about the state of the hydronephrotic kidney, and the bladder urine about the other kidney. However, due to the fact that the urine in the bladder may have been contaminated with urine from the hydronephrotic kidney, the values obtained do not exactly reflect the condition of the urine elaborated by the nonhydronephrotic kidney. Measurements performed in pyelostomy urine, however, will give such exact information about urine secreted by the hydronephrotic kidney. If there is a difference in the urine from the two kidneys, a contamination of the bladder urine will tend to minimize this difference. From the clinical observations, it can be assumed that the leakage must have been slight. Furthermore, since the aim of the study has been to investigate any difference in tubular function of the two kidneys, this error does not interfere with the conclusions which can be drawn from the results.

The technique for the collection of urine and the analytical methods were the same as those in an earlier investigation (Ericsson *et al.*, 1955), except that the carbon dioxide combining power was determined by the manometric technique of Van Slyke & Neill (1924). The total osmolarity of urine was calculated after the determination of the freezing point depression as described by Bowman, Trantham & Caulfield (1954).[1]

Results

Table 1 shows that there was no acidosis nor other signs of electrolyte imbalance. In both patients the NPN level was normal.

We are greatly indebted to Dr. Bertil Josephson, St. Eriks Hospital, Stockholm, for the performance of the determinations of the freezing point depression.

TABLE 1

Serum electrolyte values in the patients studied.

In these cases with mainly unilateral hydronephrosis there were no signs of systemic acidosis. Normal value for alkaline phosphatase at the age of the patients is below 16.

Total base mEq/l	Sodium mEq/l	Potassium mEq/l	Chloride mEq/l	Bicarbonate mEq/l	Calcium mg per 100 ml	Phosphate mg per 100 ml	Alkaline phosphatase Busch-U per 100 ml	NPN mg per 100 ml
				Case 1				
155	141	4.7	101	26.2	10.4	5.8	14	40
				Case 2				
–	134	3.7	100	24.0	11.1	6.8	13	35

Acid-base regulation in each kidney.—When the serum CO_2 combining power was stabilized at a normal level, the pH and the concentration of bicarbonate was significantly higher in the urine secreted from the hydronephrotic kidney (Figs. 1, 2). The findings in both patients indicate a defective base reabsorption in the hydronephrotic kidney. Fig. 1 demonstrates that in Case 1 during an acid load the loss of bicarbonate was reduced to a minimal level in the urine secreted both from the hydronephrotic and the nonhydronephrotic kidney. The capacity to conserve fixed base, as calculated from the decrease of the urinary pH in response to the acid load, was found to be markedly impaired in the hydronephrotic kidney. In the urine from this kidney the pH varied between 5.7 and 6.7 during the period of the acid load at the same time as the urine from the other kidney showed normal response with a decrease of the pH to 4.8.

Renal tubular function as revealed by the capacity to conserve water.—In Case 1 in response to water deprivation the osmolarity increased markedly in the bladder urine, but only slightly in the urine from the hydronephrotic kidney (Fig. 3).

In the same case the intramuscular administration of Pitressin (Parke, Davis & Co.) caused a much better response in the healthy kidney than in the hydronephrotic one, as revealed from the determinations of osmolarity of bladder and pyelostomy urine (Fig. 4). No correction was made for the possible difference in delay in the urine collection from the bladder or from the pyelostomy, either during the thirst test or during the Pitressin test.

In Case 2 the hydronephrotic kidney showed a normal capability of dilution (1.004), but an incapability of concentrating to more than 1.013 after

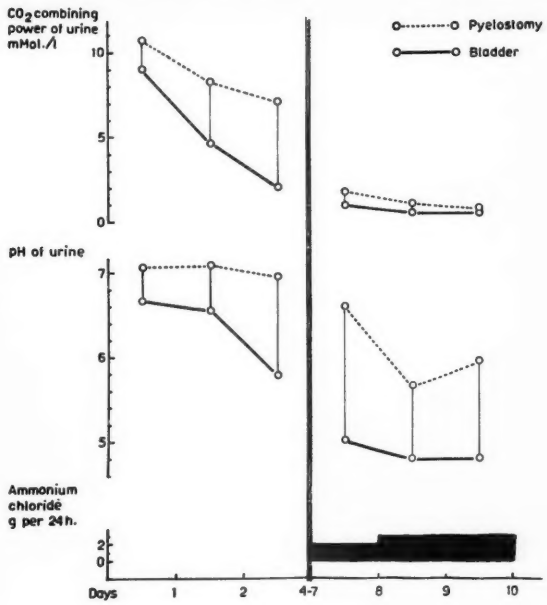

Fig. 1. *Fixed cation conservation before and during an acid load.* Case 1. Serum carbon dioxide combining power during the first and tenth day of experiment was 26.2 and 16.4 mMol/l respectively. During acid-base equilibrium excretion of bicarbonate was higher from the hydronephrotic kidney. When serum CO_2 combining power was reduced, bicarbonate excretion was at a minimum in both kidneys, but the diseased kidney acidified the urine less efficiently.

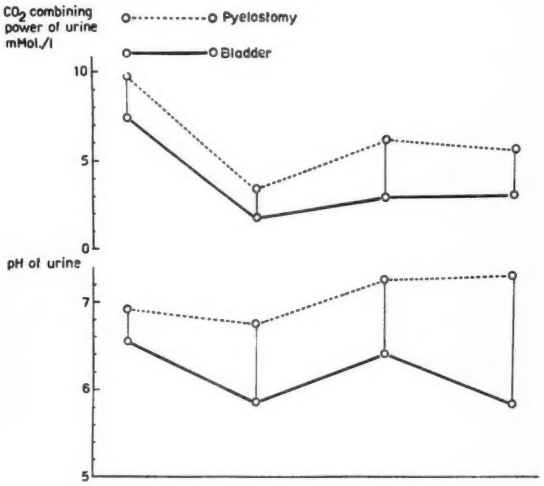

Fig. 2. *Fixed cation conservation during acid-base equilibrium determined on four different occasions.* Case 2. The hydronephrotic kidney excreted more bicarbonate than the relatively healthy one. Serum carbon dioxide combining power varied during this period between 2[illegible] and 22.9 mMol/l.

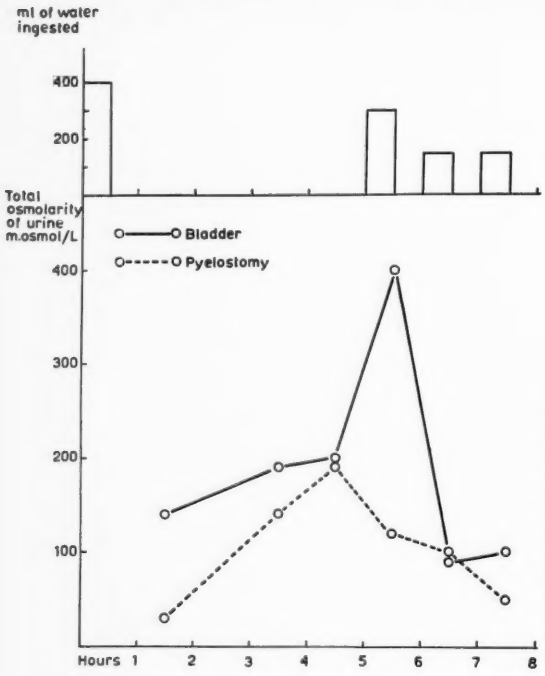

Fig. 3. *Thirst and dilution test.* Case 1. The upper section of the figure shows the amount of water ingested during the experiment; the lower section shows the osmolarity of urine collected separately from each kidney. Pyelostomy was performed on the hydronephrotic kidney. The hydronephrotic kidney conserved water less efficiently than the relatively healthy one.

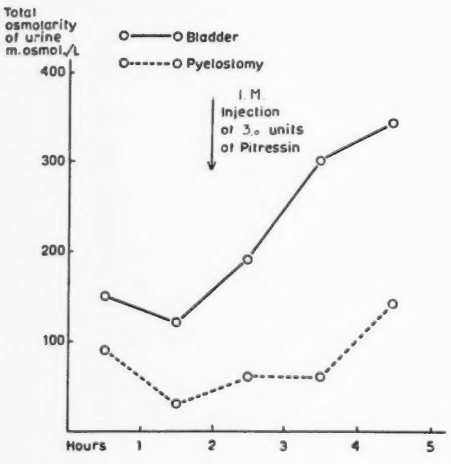

Fig. 4. *Pitressin test.* Case 1. The patient was hydrated during the entire experiment. The arrow indicates the i. m. injection of 3 pressure units of Pitressin. There was a defective response to antidiuretic hormone in the hydronephrotic kidney.

TABLE 2

Case 2. Volume and specific gravity of urine obtained from pyelostomy and bladder during 7 consecutive days.

The hydronephrotic kidney excretes large volumes of often hyposthenuric urine.

Day	Urinary volume in ml		Specific gravity		Quotient Pyelostomy/Bladder Volume
	Pyelostomy	Bladder	Pyelostomy	Bladder	
1	210	+ + +	1.007	1.026	
2	300	190	1.009	–	1.6
3	300	150	1.008	1.024	2.0
4	420	200	1.010	1.026	2.1
5	300	190	1.006	1.022	1.6
6	> 220	220	1.012	1.021	> 1.0
7	370	190	1.008	1.022	2.0

14 hours of thirst. Corresponding figures for the nonhydronephrotic kidney were 1.005 and 1.029. In this case, as can be seen in Table 2, the 24-hour urinary volume of the hydronephrotic kidney usually was much larger and the specific gravity much less than that of the nonhydronephrotic one.

The findings in Cases 1 and 2 clearly demonstrate a defective water reabsorption in the hydronephrotic kidney.

Comment

In both patients investigated there was evidence of a renal tubular damage in the hydronephrotic kidney. However, since the other kidney was functioning well, no generalized symptoms of renal tubular failure, such as chronic acidosis or a tendency to dehydration, had developed. This is in contrast to the findings in low urinary tract obstruction with bilateral hydronephrosis (Ericsson *et al.*, 1955).

In the two patients with primarily unilateral hydronephrosis, signs of renal tubular insufficiency in the hydronephrotic kidney consisted of a high bicarbonate excretion in the urine, a high urinary pH despite an acid load and a reduced capacity to reabsorb water.

The presence of only a minimal amount of bicarbonate in the urine even from the hydronephrotic kidney after an acid load seems to indicate that only a relative insufficiency with regard to bicarbonate reabsorption existed. According to modern concepts of acid-base regulation, reabsorption of bicarbonate takes place mainly in the proximal parts of the kidney tubules, but the mechanism by which the urinary pH is lowered when there is a need

of fixed base conservation is, according to the findings of Pitts and coworkers (1952), localized to the distal parts of the tubules. In Case 1 the capacity to lower the pH was impaired in the hydronephrotic kidney which points to the distal tubules as the site of the predominant damage. As revealed by the very low carbon-dioxide combining power of the urine from the hydronephrotic kidney during an increased demand for fixed base, the proximal parts of the tubules have, however, obviously maintained their capacity for bicarbonate reabsorption.

From the investigations performed, although incomplete, it seems justified to conclude impaired capability of water conservation. In the usual type of renal failure such an incapability might be seen. In that case, however, it is due to an osmotic diuresis because of loss of nephrons (Platt, 1952). In osmotic diuresis the specific gravity or osmolarity of urine never falls below that of protein-free plasma (Rapoport, Brodsky, West & Mackler, 1949), and is usually fixed about 1.010 and 330 milliosmol/liter respectively. This is in contrast to the findings in our cases where the capacity for secreting a diluted urine was retained. The excretion in Case 2 of a hypostenuric urine from the hydronephrotic kidney, at the same time as the urine from the healthy kidney is moderately concentrated, demonstrates the unsuitable handling of the water load presented to the distal parts of the tubules where the final concentration of the urine is supposed to take place.

The difference between the two kidneys in this respect might be explained by damage to the cells of the distal and perhaps also the collecting tubules (cf. Smith, 1951; Roussak & Oleesky, 1954). Further evidence in this respect is given by the decreased sensitivity to exogenous antidiuretic hormone demonstrated in Case 1. Pitressin controls water conservation probably by acting on the cells of the distal system (cf. Smith, 1951). When there is a lack of response to Pitressin, damage to these cells might be anticipated.

As stated above, the relative importance of infection and increased pressure in the renal pelvis in causing the damage still remains an unsolved problem.

Summary

From the preliminary investigation of acidification and concentration power of each kidney in two patients with predominantly unilateral hydronephrosis due to congenital ureteropelvic obstruction, the following conclusions may be drawn.

In the hydronephrotic kidney there was an impairment of the water reabsorption and a defective acid-base regulation. As maximal reabsorption of bicarbonate took place in the hydronephrotic kidney during an acid load, the proximal parts of the tubules cannot have been severely damaged. Signs of distal tubular damage were suggested by a limited capability of the kidney to lower the pH of the urine, and to produce a concentrated urine.

Études séparées des fonctionnements rénaux dans l'hydronéphrose pour la plupart unilatérale.

En se basant sur l'investigation préliminaire du pouvoir d'acidification et de concentration de chaque rein chez 2 malades avec une hydronéphrose principalement unilatérale, due à une obstruction ultéro-pelvienne congénitale, on peut tirer les conclusions suivantes : Dans le rein hydronéphrotique, il y avait une diminution dans la réadsorption d'eau et une régulation défectueuse de la base d'acide. Etant donné qu'une réadsorption maxima de bicarbonate s'observe dans le rein néphrotique pendant une charge d'acide, les parties voisines des tubules ne peuvent pas être sérieusement lésées. Une possibilité réduite du rein pour abaisser le pH de l'urine et pour produire une urine concentrée font penser à une détérioration du tubule distal.

Gesonderte Nierenfunktions-Studien bei vorwiegend unilateraler Hydronephrosis.

Auf Grund einer vorläufigen Untersuchung betreffend Säuerung und Konzentrationsvermögen der beiden Nieren zweier Patienten mit vorwiegend unilateraler Hydronephrosis, verursacht durch congenitalen Ureter-Nierenbecken-Verschluss, können folgende Schlussfolgerungen gezogen werden:

In der hydronephrotischen Niere bestand eine verschlechterte Wasserrückresorption und eine defekte Säure-Basen-Regulation. Eine maximale Rückresorption von Bikarbonat fand während einer Säurebelastung in der hydronephrotischen Niere statt, die proximalen Teile der Tubuli können also nicht ernstlich beschädigt worden sein. Ein Schaden an den distalen, tubulären Teilen wird vermutet, da die Niere nur eine begrenzte Fähigkeit zur Herabsetzung des pH des Urins sowie zur Produktion eines konzentrierten Urins aufwies.

Estudios de la función renal por separado en hidronefrosis predominantemente unilaterales.

Del estudio preliminar de la capacidad de acidificación y concentración de cada riñón, en dos pacientes con hidronefrosis predominantemente unilateral por obstrucción congénita ureteropélvica, se desprenden las siguientes conclusiones.

En el riñón hidronefrótico existía un transtorno de la reabsorción hídrica y una regulación acido-base deficitaria. Las porciones proximales de los túbulos no podían estar gravemente lesionados ya que tuvo lugar una reabsorción de bicarbonato máxima, en el riñón hidronefrótico, durante la sobrecarga ácida. La limitación de la capacidad del riñón para descender el pH de la orina, y segregar una orina concentrada sugerían la existencia de lesiones tubulares distales.

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Respiratory Studies in Children

IV. The Effect of Bronchodilator Drugs on the Lung Volumes in Symptom-free Asthmatic Children[1]

by SVEN KRAEPELIEN

Earlier published studies have shown that the lung volume conditions of asthmatic patients, adults and children alike, differ even in many cases during their symptom-free intervals from the conditions of healthy individuals (1, 2, 8, 9, 12). This indicates that the disturbances of the pulmonary function during an acute attack are in many patients not completely reversible. In a recently published study of 98 asthmatic children was shown that in symptom-free periods the functional residual capacity and the residual volume are increased and that the degree of these changes is related to the frequency of the attacks (11). Even if a hyperinflation of the lungs is demonstrable in a symptom-free asthmatic, the reason for this condition is not immediately apparent. The changes may be either of a functional character, occasioned solely by a bronchial obstruction or by an emphysema, by which is meant in this context "a pathological condition of the lung characterized by reduction or loss of elastic fibers, tearing of alveolar septa and decrease in the pulmonary bed" (5).

The nature of the changes can be studied by examining the pulmonary function before and after administration of different bronchodilator drugs. Several investigations of this kind have been conducted on symptom-free adult asthmatics (2, 8, 10). Lucas (1951) made a study of six symptom-free asthmatic children aged 11–15 years and showed that the pulmonary function could be improved by the administration of epinephrine HCl subcutaneously or Vaponefrin by nebulizer (12). Since these six cases of Lucas are the only ones recorded in the literature, it was deemed desirable to study a larger group of asthmatic children—with increased residual volume—and to investigate the lung volumes before and after administration of

[1] Aided by a grant from the Swedish National Association against Tuberculosis and Other Social Diseases.

different bronchodilator drugs, Isoprenaline in aerosol form and Aminophylline (theophylline ethylenediamine) intravenously, in order to get further informations of the genesis of the disturbances.

Definitions and Nomenclature

For definitions and nomenclature reference may be made to an earlier paper in this series (7).

Material

The material for this study was taken from the Allergic In-patient and Out-patient Departments at the Pediatric Clinic of Karolinska Sjukhuset, Stockholm. All children were well-known to the examiner. Their ages ranged from 6 to 15 years; fifteen of them (ten boys and five girls) were examined before and after inhalation of an Isoprenaline solution, and fifteen (ten boys and five girls) before and after intravenous administration of Aminophylline.

Most of the children (24 cases) had taken part in the previous cross-section study of asthmatic children (11). Five come into both series of this study.

The material was chosen from children who, when previously examined, had shown an elevation of the ratio residual volume to total lung capacity (V_R/V_{TLC}), i.e. outside 95 per cent confidence intervals for V_R/V_{TLC} in healthy children (Fig. 1). The ratio functional residual capacity to total lung capacity (V_{FRC}/V_{TLC}) for the majority of the children was also outside 95 per cent confidence intervals (Fig. 2).

At the time of examination no child displayed clinical symptoms of asthma, subjectively or objectively, nor had any child received symptomatics in any form during the three days prior to the examination.

The age distribution within the respective series is shown in Fig. 1. The children complied with Broman, Dahlberg and Lichtenstein's normal values of physical development for Swedish children, based on age, height and weight (3), with the exception of one child in each series who was outside the 95 per cent confidence intervals as regards the relation length to age.

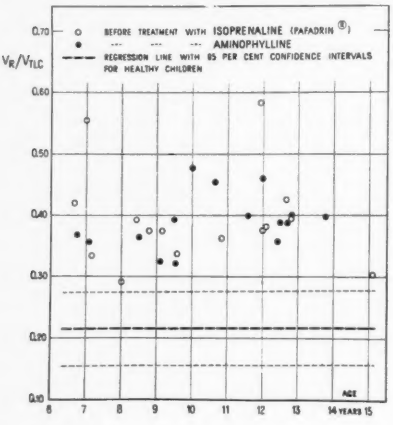

Fig. 1. The ratio of residual volume to total lung capacity (V_R/V_{TLC}) in relation to age before administration of Isoprenaline and Aminophylline. The regression line with 95 per cent confidence intervals for healthy children is drawn.

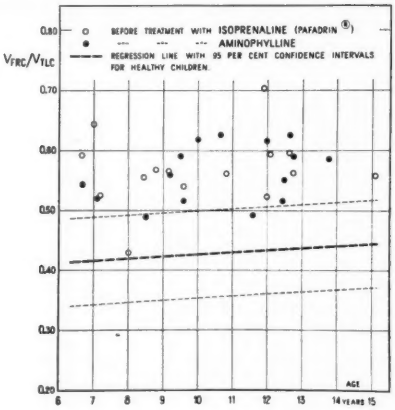

Fig. 2. The ratio of functional residual capacity to total lung capacity (V_{FRC}/V_{TLC}) in relation to age before administration of Isoprenaline and Aminophylline. The regression line with 95 per cent confidence intervals for healthy children is drawn.

Method and Procedure

The functional residual capacity (V_{FRC}) was determined in a closed system with helium as test gas. The apparatus, method and calculations have been described in an earlier paper (7).

The procedure adopted was as follows. To obtain starting values a duplicate determination was made of the different lung volumes. Immediately thereafter the children were given Isoprenaline or Aminophylline.

The Isoprenaline was given in aerosol form from a 1 per cent solution (Pafadrin®), using a Pari-Optimal inhalator, model Primus.[1] The inhalation time was 30 seconds, which clinical experience shows to be the time generally required with this apparatus to achieve a distinct alleviation of acute asthmatic attacks. After inhalation the children rested for 15–20 minutes, after which a renewed duplicate determination of the lung volumes was performed.

Aminophylline was given intravenously as a 2.5 per cent solution in doses of 0.19–0.27 (mean 0.23) ml per kg body weight. This dose was of an order of magnitude which, according to clinical experience, renders distinct help to children suffering from acute asthmatic trouble. A second duplicate determination of the lung volumes was performed after 30–35 minutes of rest.

Every duplicate determination took about 40–45 minutes. The determinations of lung volumes were technically satisfactory in all 60 duplicate tests.

Random Error of the Method

The random error of the method for each lung volume determined was calculated from the differences between the duplicate determinations according to Dahlberg (6). Before carrying out the calculation, an investigation was made as to whether the effect of the respective drugs had increased or diminished in the interval between

[1] Manufacturer: Paul Ritzau Pari-Werk, Starnberg am See, Oberbayern. Drop size 0.5–5 μ, majority 1–2 μ. About 0.4 ml Isoprenaline solution is nebulized in 30 secs.

TABLE 1

The random error of the method in the determination of lung volumes.

	Before Isoprenaline and Aminophylline			After Aminophylline			After Isoprenaline		
	V_{FRC}	V_R	V_{VC}	V_{FRC}	V_R	V_{VC}	V_{FRC}	V_R	V_{VC}
Number of double determinations	30	30	30	15	15	15	15	15	15
Mean difference (d), liters	+0.01	±0.00	+0.01	+0.03	+0.02	−0.01	+0.01	+0.02	+0.0
Standard deviation of the differences (σ_d), liters	±0.099	±0.091	±0.106	±0.073	±0.072	±0.040	±0.134	±0.137	±0.0
Error in the mean difference (ε_d), liters	±0.018	±0.017	±0.019	±0.019	±0.019	±0.010	±0.035	±0.035	±0.0
$t = d/\varepsilon_d$	0.56	0.00	0.53	1.58	1.05	1.00	0.29	0.57	1.8
P	>0.2	>0.2	>0.2	0.2>P >0.05	>0.2	>0.2	>0.2	>0.2	0.2> >0.0
Standard deviation in an individual determination (σ_x), liters	±0.070	±0.064	±0.075	±0.052	±0.051	±0.028	±0.095	±0.097	±0.0
Mean of all double determinations ($\bar{x}$), liters	2.02	1.41	2.15	1.90	1.25	2.16	1.98	1.28	2.1
Coefficient of variation $(\sigma_x \times 100)/\bar{x}$	±3.5 %	±4.5 %	±3.5 %	±2.7 %	±4.1 %	±1.3 %	±4.8 %	±7.6 %	±1.7

the two tests. No significant difference was demonstrable (Table 1). Therefore the mean of the two post-treatment determinations may be considered representative of the respective lung volumes in the individual case.

The random error of the method was calculated on the two series independently after the treatment (see Table 1). The coefficients of variation proved to be of about the same order of magnitude as the values obtained before the administration and as the values previously obtained for healthy children.

Results

As in the earlier studies in this series, the respective lung volumes have been correlated to body height, and the ratios V_{FRC}/V_{TLC} and V_R/V_{TLC} have been correlated to the age. No division has been made between the sexes. The lung volumes before and the changes found after administration are shown for each individual case in Table 2.

The influence of the two drugs in each individual case has been calculated from the percentual change in the lung volumes after administration. The mean differences were tested against zero (t-test) and were found significant as regards V_R, V_{VC} and V_R/V_{TLC}, both in the Isoprenaline and in the Aminophylline series. A significant difference is likewise found as regards V_{FRC}

TABLE 2

Lung volumes in litres before administration (a) and the changes found after administration (b) of Isoprenaline and Aminophylline.

Case no.	V_{FRC}		V_R		V_{TLC}		V_{VC}	
	a	*b*	*a*	*b*	*a*	*b*	*a*	*b*
				ISOPRENALINE				
1	2.84	−0.08	2.00	−0.11	5.04	+0.01	3.05	+0.11
2	3.40	−0.30	2.45	−0.51	6.52	−0.26	4.08	+0.24
3	1.75	−0.55	1.51	−0.62	2.72	−0.62	1.21	0
4	2.66	−0.05	1.72	+0.02	4.49	+0.08	2.77	+0.07
5	1.09	−0.06	0.74	−0.12	2.54	+0.16	1.80	+0.28
6	2.48	−0.34	1.61	−0.36	4.43	−0.07	2.83	+0.28
7	1.15	−0.05	0.74	−0.06	2.19	−0.11	1.45	−0.05
8	2.44	+0.01	1.34	+0.05	4.40	+0.19	3.07	+0.13
9	3.16	−0.10	2.63	−0.36	4.51	−0.02	1.88	+0.34
10	1.70	+0.07	1.06	+0.04	3.15	+0.15	2.09	+0.11
11	1.66	−0.01	1.10	−0.03	2.95	+0.13	1.85	+0.16
12	1.51	−0.06	1.07	−0.08	2.72	−0.06	1.66	+0.01
13	1.55	−0.03	1.10	−0.11	2.62	+0.04	1.52	+0.15
14	1.70	−0.12	1.13	−0.15	3.00	−0.02	1.88	+0.12
15	2.52	−0.25	1.80	−0.34	4.24	−0.11	2.45	+0.23
				AMINOPHYLLINE				
1	1.66	+0.05	0.97	+0.08	2.95	+0.11	1.97	+0.04
2	2.87	−0.04	2.16	−0.10	4.65	−0.02	2.49	+0.08
3	1.59	−0.14	1.12	−0.21	2.89	−0.08	1.76	+0.13
4	1.42	−0.08	1.06	−0.15	2.90	−0.03	1.84	+0.12
5	1.24	−0.13	0.84	−0.12	2.38	−0.10	1.55	+0.01
6	2.11	−0.12	1.33	0	3.39	−0.07	2.05	−0.06
7	1.80	+0.04	1.13	−0.02	3.49	−0.12	2.27	0
8	3.00	−0.11	2.06	−0.11	5.09	−0.17	3.04	−0.07
9	1.97	−0.08	1.43	−0.25	2.15	+0.05	1.72	+0.30
10	2.16	−0.12	1.69	−0.33	3.50	−0.03	1.81	+0.29
11	1.87	+0.04	1.51	−0.25	3.81	+0.10	2.30	+0.35
12	2.10	+0.08	1.40	−0.02	3.56	+0.11	2.17	+0.12
13	1.36	+0.08	0.94	+0.06	2.52	+0.19	1.58	+0.12
14	1.73	+0.09	1.18	−0.05	3.35	−0.01	2.17	+0.05
15	2.21	−0.13	1.50	−0.05	3.79	−0.07	2.29	−0.02

and the ratio V_{FRC}/V_{TLC}, but only after Isoprenaline medication. No difference in V_{TLC} was found in any of the series (Table 3).

To get a general idea of these changes, the material was also treated as a group. The Isoprenaline and Aminophylline series were statistically analysed, as in the earlier studies, by the Snedecor method of regression calculation (13) both before and after administration of the drugs. The

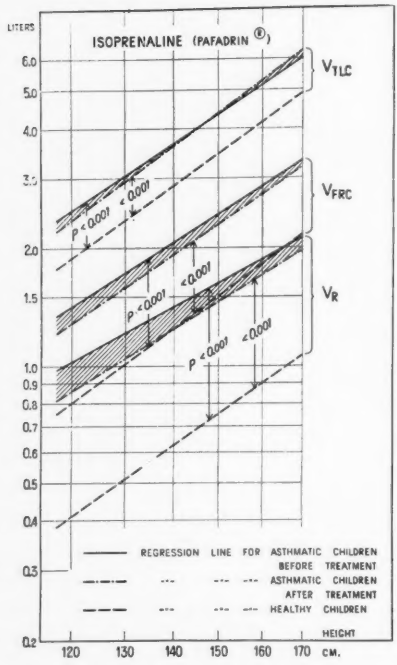

Fig. 3. Regression lines for total lung capacity (V_{TLC}), functional residual capacity (V_{FRC}) and residual volume (V_R) in relation to height before and after administration of Isoprenaline. The regression lines for healthy children are also drawn. The significance of differences in distances between the regression lines is designated (in view of the probability that the two regression lines belong to the same sample).

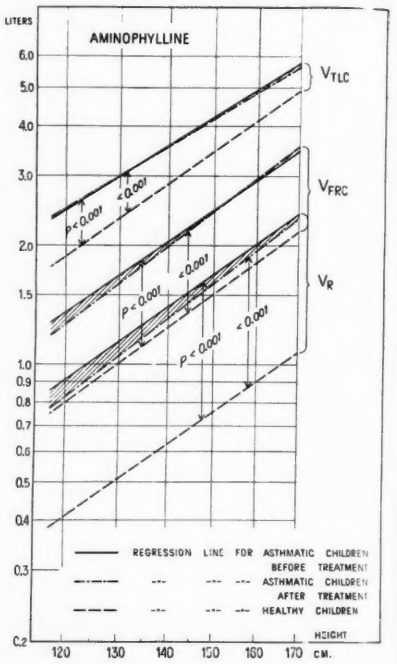

Fig. 4. Regression lines for total lung capacity (V_{TLC}), functional residual capacity (V_{FRC}) and residual volume (V_R) in relation to height before and after administration of Aminophylline. The regression lines for healthy children are also drawn. The significance of differences in distances between the regression lines is designated (in view of the probability that the two regression lines belong to the same sample).

resulting regression lines, and the corresponding regression lines for healthy children, are shown in Figs. 3–6.

In the first place the regression lines before and after administration were tested against the corresponding lines for healthy children by covariance analysis. No differences were found in the slope of the regression lines, but there were significant differences in the distance between the lines for V_{FRC}, V_R, V_{TLC}, V_{FRC}/V_{TLC} and V_R/V_{TLC} in both series, both before and after administration. No deviation was found in the regression lines for V_C, however, either in respect to slope or distance.

On the other hand, in no series was a significant difference found in the

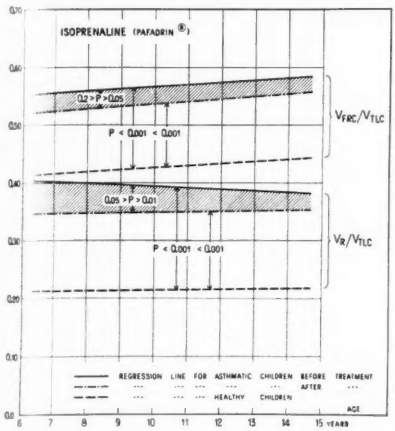

Fig. 5. Regression lines for the ratios of functional residual capacity to total lung capacity (V_{FRC}/V_{TLC}) and residual volume to total lung capacity (V_R/V_{TLC}) in relation to age before and after administration of Isoprenaline. The regression lines for healthy children are also drawn. The significance of differences in distances between the regression lines is designated (in view of the probability that the two regression lines belong to the same sample).

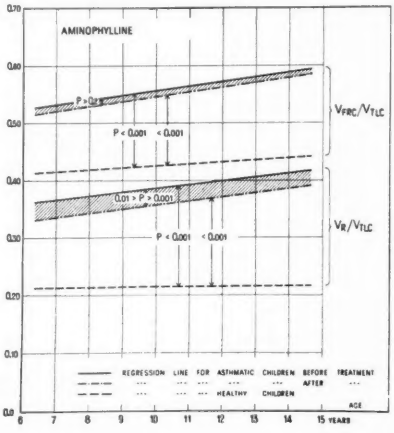

Fig. 6. Regression lines for the ratios of functional residual capacity to total lung capacity (V_{FRC}/V_{TLC}) and residual volume to total lung capacity (V_R/V_{TLC}) in relation to age before and after administration of Aminophylline. The regression lines for healthy children are also drawn. The significance of differences in distances between the regression lines is designated (in view of the probability that the two regression lines belong to the same sample).

TABLE 3

The mean percentual change in lung volumes in the individual cases after administration of Isoprenaline and Aminophylline, and testing of significance (t-test).

	Isoprenaline		Aminophylline	
	Mean of percentage diff.		Mean of percentage diff.	
V_{FRC}	− 6.04	$0.02 > P > 0.01$	− 1.93	$P > 0.1$
V_R	− 11.44	$0.01 > P > 0.001$	− 7.97	$0.01 > P > 0.001$
V_{VC}	+ 5.35	$0.01 > P > 0.001$	+ 5.05	$0.02 > P > 0.01$
V_{TLC}	− 1.07	$P > 0.1$	− 0.55	$P > 0.1$
V_R/V_{TLC}	− 11.12	$P < 0.001$	− 6.98	$0.01 > P > 0.001$
V_{FRC}/V_{TLC}	− 7.94	$0.02 > P > 0.01$	− 1.82	$0.1 > P > 0.05$

distance between the various regression lines before and after administration, with the exception of V_R/V_{TLC} in both series. In both series, however, there is a tendency to normalization of V_R, V_{FRC} and V_{FRC}/V_{TLC}. The increase in V_R and V_{FRC} in relation to healthy children is 20 per cent and 14 per cent

less respectively after administration of Isoprenaline and 11 per cent and 4 per cent less respectively after Aminophylline. (The calculations were made on the centre point of the regression lines for a body height of 145 cm.) The corresponding figures for the ratios V_R/V_{TLC} and V_{FRC}/V_{TLC} are 25 per cent and 21 per cent for Isoprenaline, and 17 per cent and 8 per cent for Aminophylline (at the centre point of the respective regression lines, 10.5 years).

Discussion

The bronchodilator drugs used for the present investigation were Isoprenaline, belonging to the adrenaline group, and Aminophylline, belonging to the xanthine group. The bronchodilatory action of these drugs is well known. Isoprenaline is administered in aerosol form by inhalation, so that its effect on bronchi and bronchial mucous membrane may be regarded as local, whereas the effect of Aminophylline is more general. The extent of the effect of Aminophylline on the pulmonary circulation, and hence on the pulmonary function, as a result of its cardiovascular action, is difficult to assess. Herschfus *et al.* (10), however, consider that these two drugs have very little cardiovascular action.

The study has shown that asthmatic children who manifest signs of hyperinflation of the lungs during periods when asthmatic symptoms are absent continue to show hyperinflatory signs after treatment with bronchodilator drugs (Isoprenaline and Aminophylline), though less pronounced than before the treatment. The normalizing effect of these drugs on the lung volumes, even if comparatively slight, suggests that the hyperinflation is, at least to some degree, of a functional character, caused by a bronchial obstruction. This obstruction may be of various types: some of the airways may be totally obstructed (with lowered V_{VC} in consequence) whereas others are normal or only partially closed off; or all the airways may be obstructed to some extent, but none completely. Since V_{VC} does not significantly deviate from the conditions in healthy children, there is reason to suppose that most of the bronchial obstruction in symptom-free asthmatic children consists of a general partial obstruction, even if the possibility of minor total obstructions cannot be ruled out. The latter eventuality is suggested by the small yet significant increase in V_{VC} found in calculations in individual cases.

Even if volumes and ratios after administration of the drugs approach the conditions in healthy children, they are still clearly pathological. The explanation may be either that the drugs have not entirely released the bronchial obstruction, but have had merely a partial effect, or that the changes are caused both by a bronchial obstruction and by a parenchymal

change as in an emphysema. But how much the changes after the treatment are caused by one or the other is not made clear by this study. A more intense treatment with bronchodilator drugs over a longer period might, however, release the bronchial obstruction better than the sporadic administration that has been used in this investigation. Cander & Comroe have shown that the pulmonary function of adults suffering from asthmatic symptoms is helped more by a combination of Isoprenaline (inhalation) and Aminophylline (intravenous) than by Isoprenaline alone (4). On the same analogy it is conceivable that the bronchodilator effect, even in symptom-free asthmatic children, would be enhanced if a preparation in aerosol form, having a direct action on the bronchi and bronchial mucous membrane, were combined with a preparation having more systemic action (intravenous administration).

Since asthmatic children, even when free of symptoms, show signs of a bronchial obstruction which can be influenced by bronchodilator drugs, this is quite naturally a significant factor in the therapy. Consequently, in addition to the general anti-allergic treatment, prolonged treatment with bronchodilator drugs should diminish the risk of parenchymal injury in asthmatic children who manifest a hyperinflation of the lungs during symptom-free periods.

Summary

1. The lung volumes of symptom-free asthmatic children (6–15 years) with elevated ratio of residual volume to total lung capacity were studied before and after administration of bronchodilator drugs. Fifteen children (ten boys and five girls) were given Isoprenaline (Pafadrin®) in aerosol form, and fifteen (ten boys and five girls) Aminophylline intravenously.

2. A significant lowering of residual volume, functional residual capacity (only after Isoprenaline) and vital capacity was observed after administration of the drugs, but there were still distinct signs of hyperinflation. The effect appeared to be greater after Isoprenaline than after Aminophylline.

3. The results suggest that the observed changes in the lung volumes of symptom-free asthmatic children are partly of functional origin.

4. Emphasis is placed on the importance of prolonged treatment with bronchodilator drugs, even during symptom-free periods.

Etude de la respiration chez l'enfant

IV. *Effets de substances broncho-dilatatrices sur les volumes pulmonaires d'enfants asthmatiques sans symptômes respiratoires.*

Les volumes pulmonaires d'enfants asthmatiques, âgés de 6 à 15 ans, sans symptôme respiratoire, mais avec un volume résiduel élevé (par rapport à la capacité pulmonaire totale) ont été étudiés avant et après administration de substances broncho-dilatatrices. Quinze enfants (10 garçons et 5 filles) ont reçu de l'Isoprenaline (Pafadrin®) dans un

aérosol, et quinze enfants (10 garcons et 5 filles) ont reçu de l'Aminophylline par voie intra-veineuse. Après administration d'Isoprenaline, on observe une diminution significative du volume résiduel, de la capacité résiduelle fonctionnelle et de la capacité vitale; après l'injection d'Aminophylline, seuls la capacité vitale et le volume résiduel sont diminués significativement. Dans les deux cas, il persiste cependant des signes nets d'hyper-expansion. Il semble que l'effet de l'Isoprenaline soit plus marqué que celui de l'Aminophylline. Ces résultats incitent à penser que les modifications des volumes pulmonaires chez les enfants asthmatiques sans symptôme respiratoire, sont, partiellement du moins, d'origine fonctionnelle. Les auteurs mettent en évidence l'importance d'un traitement prolongé à l'aide de substances broncho-dilatatrices, même pendant les périodes où il n'existe aucun symptôme respiratoire.

Atmungsstudien bei Kindern.

IV. *Die Wirkung von bronchienerweiternden Mitteln auf das Lungenvolumen bei symptomfreien asthmatischen Kindern.*

Bei symptomfreien asthmatischen Kindern (6–15 Jahre alt), die ein erhöhtes Verhältnis von Residualvolum zu totaler Lungenkapazität aufwiesen, wurden die Lungenvolumina vor und nach Zufuhr von bronchienerweiternden Mitteln untersucht. 15 Kindern (10 Knaben und 5 Mädchen) wurde Isoprenaline (Pafadrin®) als Aerosol und 15 weiteren Kindern (10 Knaben und 5 Mädchen) Aminophylline i.v. zugeführt. Nach der Zufuhr der Pharmaka wurde eine signifikante Verminderung des Residualvolumens, der funktionellen Residualkapazität (nur nach Isoprenaline) und der Vitalkapazität beobachtet, doch lagen weiterhin klare Zeichen einer Überblähung vor. Die Wirkung scheint grösser nach der Zufuhr von Isoprenaline als von Aminophylline zu sein. Die Ergebnisse sprechen dafür, dass die beobachteten Veränderungen der Lungenvolumina bei symptomfreien asthmatischen Kindern wenigstens teilweise funktionell bedingt sind. Die Bedeutung einer langdauernden Behandlung mit bronchienerweiternden Mitteln auch während symptomfreier Perioden wird hervorgehoben.

Estudio de la respiración en la infancia.

IV. *Efectos de las drogas broncodilatadoras sobre el volumen pulmonar en niños asmáticos sin síntomas respiratorios.*

Los volúmenes pulmonares de niños asmáticos, de 6 a 15 años, sin síntomas respiratorios, pero con un volumen residual elevado (en relación a la capacidad pulmonar total) fueron estudiados antes y después de la administración de substancias broncodilatadoras. 15 niños (10 varones y 5 niñas) recibieron Isoprenaline (Pafadrin®) en aerosol y otros 15 (10 varones y 5 niñas) Aminofilina por vía intravenosa. Luego de la administracíon de Isoprenaline se observó una significativa disminución del volumen residual, de la capacidad residual funcional y de la capacidad vital; luego de la inyección de Aminofilina, solamente la capacidad vital y el volumen residual sufrieron una disminución de significación. En ambos casos persistieron sin embargo, signos de hiperexpanción. Parece ser que los efectos de la Isoprenaline son más marcados que los de la Aminofilina. Estos resultados llevan a pensar que las modificaciones de los volúmenes pulmonares en los niños asmáticos sin síntomas respiratorios sean parcialmente de origen funcional. Los autores destacan la importancia de un tratamiento prolongado con drogas broncodilatadoras, aún durante aquellos intervalos libres de síntomas respiratorios.

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Respiratory Studies in Children

V. Maximal Breathing Capacity in Healthy and in Symptom-free Asthmatic Children, 7-14 Years of Age[1]

by INGA ENGSTRÖM, PETTER KARLBERG, SVEN KRAEPELIEN and GISELA WENGLER

The impairment of the ventilation during an asthma attack due to bronchospasm, swelling of the mucous membrane and increased secretion is well known. The increased resistance of the airways, the role of which is greatest during expiration, causes this phase to be prolonged and so has a greater influence at high breathing rates. In assessing the ventilation of asthmatics, therefore, a test should be used which takes account of the time factor. One such test is the maximal breathing capacity (MBC), defined as the maximal volume of gas that can be breathed per minute (4).

Since the introduction of the method by Hermanssen in 1933 (13), it has been widely used for examination of adults, and a lowered MBC has been found in asthmatics even in symptom-free periods (1, 2, 12, 14). Several studies of MBC in healthy children have been published in recent years (10, 11, 15, 18, 21, 22). The only study of MBC in asthmatic children that we have found is Lucas' account (1951) relating to six asthmatic children (17).

In our respiratory studies of symptom-free asthmatic children we considered it desirable to test the applicability of this method for determination of the pulmonary function. As it requires a well standardized technique and good cooperation from the patient, we found it necessary to gain experience by working also on a group of healthy children with the same apparatus and under the same experimental conditions. The MBC is often correlated to the resting minute volume ($\dot{V}$) in calculations of the breathing reserve (BR). Therefore this determination as well has been included in the study.

Material

The material comprises 46 healthy children in the ages 7–14 years, 24 boys and 22 girls, and 19 asthmatic children in the same age range, 16 boys and 3 girls. The healthy

[1] Aided by a grant from the Swedish National Association against Tuberculosis and Other Social Diseases.

children were selected from a school at random with roughly the same number in each age group. The asthmatic children were selected and clinically classified as in a previous study (16). Five of the children belonged to Group 3, with more than 10 attacks per year or long status asthmaticus, four to Group 2, with 5–10 attacks per year, and ten to Group 1, with less than 5 attacks per year. All were symptom-free at the time of the examination and had not been given any symptomatic treatment during the preceding three days. The childrens physical development as regards height and weight was within the 95 per cent confidence limits found in healthy Swedish children (3) with the exception of one asthmatic girl, whose weight was low for her height.

Method and Procedure

With the nose closed by a nose clip the child breathed room-air through a mouthpiece via an Enghoff valve specially adapted to high ventilation rates and volumes (8). From the outlet of the valve the expired air was led via a 35 mm rubber tube and a three-way stop cock into a freely suspended plastic bag with a capacity of about 40 litres. The resting minute volume was obtained by collecting the expired air during two-minute periods. For the determination of the MBC the child was strongly encouraged to breathe as much as possible for 15 secs., during which time the air was collected. It was left to the child itself to choose the rate and the depth of breathing. The volume of the expired air collected in the bag was determined by emptying the bag by means of a pump through a gas meter. The figures obtained were converted to minute volumes and corrected to BTPS.

The children came for the examination directly from school or directly from the Allergy Outpatient Department. Before the determination started the child rested in a comfortable chair for about 10 minutes. After a short period to allow the child to become accustomed to breathing through the apparatus, the resting minute volume was determined during three 2-minute periods. Thereafter the MBC was determined three times with five minutes' rest between determinations.

Random Error of the Method and Calculations

The random error of the method was calculated according to Dahlberg (6), from the differences between the first two figures for resting minute volume and between the two highest figures for MBC (Table 1). From the statistical analysis no difference was found between the healthy and the asthmatic children, and the two groups were therefore combined. The table shows no significant difference between the first and the second determination of resting minute volume. The coefficient of variation of resting minute volume was found to be as high as ± 12.5 per cent. We considered the mean value of three determinations, however, to be representative.

No significant difference was found between the two highest values of MBC (Table 1), indicating that three determinations would be sufficient. The coefficient of variation was found to be $\pm 6{,}1$ per cent. The mean of the two highest values of the three determinations was considered to be representative for an individual case with conformity to calculation of vital capacity (9). The breathing reserve (BR) was calculated from the values of maximal breathing capacity (MBC) and resting minute volume ($\dot{V}$), using the formula $[(\text{MBC} - \dot{V})/\text{MBC}] \times 100$.

TABLE 1

The random error of the method in determination of maximal breathing capacity (MBC) *and resting minute volume* ($\dot{V}$).

	MBC	$\dot{V}$
Number of double determinations	65	65
Mean difference (d), liters	0,7	−0,29
Standard deviation of the difference (σ_d), liters	±5,7	±1,2
Error in the mean difference (ε_d), liters	±0,71	±0,15
$t = d/\varepsilon_d$	0,99	1.93
P	>0,10	<0.10<0.05
Standard deviation in an individual determination (σ_x), liters	±4,03	±0.86
Mean of all double determinations ($\bar{x}$), liters	66,4	7.1
Coefficient of variation $(\sigma_x \times 100)/\bar{x}$	±6,07 %	±12.05 %

Results

The results are shown graphically in Fig. 1, where both resting minute volume and MBC correlated to height are plotted on a double logarithmic scale with the values for healthy and asthmatic children differently marked. No sex differentiation has been made in this study since in the large material examined by Ferris *et al.* no marked difference between boys and girls was found (10, 11). The chart shows good correlation between MBC and body height, but poor correlation between resting minute volume and body height.

The corresponding regression lines for MBC of healthy and asthmatic children are drawn in the figure, calculated according to Snedecor (20). The correlation with body height is statistically significant, tested on the values of the healthy children. The 95 per cent confidence intervals is from +42 to −29 per cent around the regression line.

The values of BR are plotted in Fig. 2 in relation to height on a metric scale. The reason for using a metric scale was that BR is expressed as a percentage. The figure shows a tendency to correlation between MBC and body height, why regression calculations were carried out. The regression lines for healthy and asthmatic children are drawn on the chart, and the line for the healthy children also shows a slight slope. However, BR was not found to be statistically significantly correlated to body height. Thus the mean of the values was calculated for the healthy children and was found to be 90.0 per cent (with 95 per cent confidence intervals of 82.5–97.5 per cent). The corresponding mean value for the symptom-free asthmatic children is 86.7 per cent.

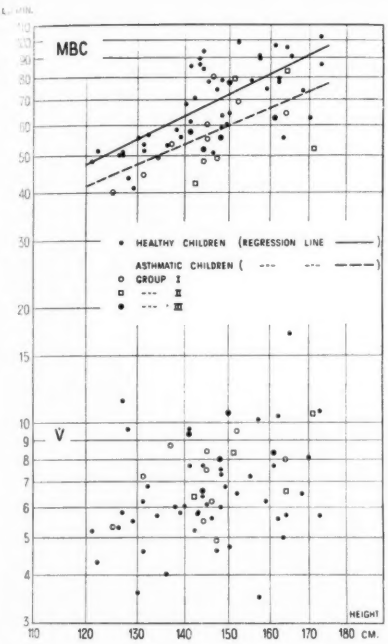

Fig. 1. MBC and resting minute volume ($\dot{V}$) in relation to body height on a double logaritmic plot. The regression lines for MBC are drawn for the healthy children and the asthmatic children from the equations $MBC = 6.93 \times 10^{-3} \times H^{1.844}$ and $MBC = 1.60 \times 10^{-2} \times H^{1.642}$ respectively.

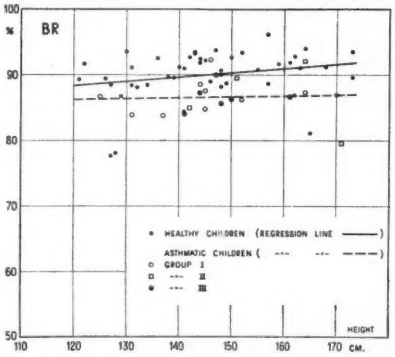

Fig. 2. The breathing reserve (BR) in relation to body height on a metric scale. The regression lines are drawn for the healthy children and the asthmatic children from the equations $BR = 0.0624 \times H + 80.9$ and $BR = 0.0132 \times H + 84.7$ respectively.

The regression line for MBC of asthmatic children is below that for healthy children (Fig. 1). The difference in distance was statistically tested by covariance analysis and found to be significant ($P < 0.01$). The resting minute volumes of asthmatic children, considered as a group, tend to be higher than those of healthy children. No statistical analysis was made, however, owing to the heavy fluctuations in the values. As regards BR, the mean value for asthmatic children as a group is significantly lower (t-test, $P < 0.01$). Some of the asthmatic children, however, show values corresponding to those found in healthy children, both for MBC and BR.

Discussion

It has been possible to determine the maximum breathing capacity of children in the range 7–14 years with a coefficient of variation of ± 6 per cent, which must be considered a good result in view of the cooperation required of the child. In this error, which was calculated from differences between duplicate determinations in individual cases, the variations due to differences in rate and depth of breathing should not be so marked. Each individual may be presumed to employ roughly the same breathing technique

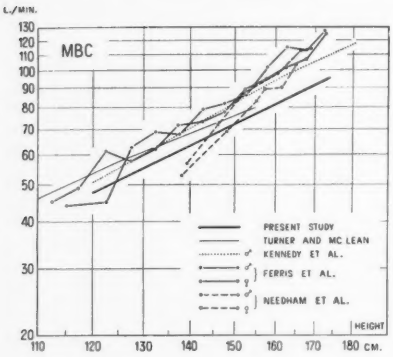

Fig. 3. Regression line for MBC in healthy children in relation to body height on a double logarithmic plot, compared with the results of other authors.

in the closely following examinations. In a comparison between different individuals, on the other hand, these factors must acquire greater importance (7). Since MBC is a functional test, expressed in absolute units, the comparative values between different individuals should be related to body size, at least during childhood. The regression equations for healthy children also show a correlation to body size, judged by body height. Even if this correlation is taken into account, the variations between individuals are considerable. As an example, the 95 per cent confidence intervals for children of body height 145 cm is 97–48 litres per minute.

Further difficulties in the determination of MBC appear when comparing the values with those of previous authors. This comparison is shown graphically in Fig. 3, and our values are seen to be slightly lower throughout. The difference is probably due to the method employed (15, 18). Among the studies used for comparison, Turner & McLean (22), Ferris *et al.* (10, 11), and Kennedy *et al.* (15) have employed spirometry, while Needham *et al.* (18) employed Douglas bags. The values closest to ours are those of Needham *et al.*, whose method resembles ours in principle.

The great variation in values within and between different series proves the importance, in every study of a pathological material, of adapting the method to a control material of healthy subjects.

If MBC is correlated to resting minute volume by calculation of BR, a relative figure of the pulmonary ventilation capacity is obtained which has not been found to be significantly correlated to body height. Whether the accuracy is thereby increased is difficult to say, since an additional large error of method is introduced through the determination of resting minute volume. Our mean value of BR (90 per cent) is nevertheless in good agreement with Turner & McLean's 89.7 per cent in children (22) and Cournand's 91.7 per cent in adults (5).

Comparing the symptom-free asthmatic children with healthy children, the values both of MBC and of BR are statistically significantly lower. This applies to asthmatic children as a group. An assessment of individual cases is made difficult, however, by the great variations among the healthy children. Most of the asthmatic children in our material belong to Group 1, that is the group with mildly asthmatic cases. This may be the reason why the difference is not greater. There would perhaps be a more distinct difference if more of the children belonged to Group 3. However, in agreement with Schiller & Lowell (19) we are of the opinion that this method is not especially well adapted to severe, symptomfree cases of asthma, since it places a strain on the patient and involves a risk of asthmatic symptoms being provoked by the hyperventilation.

The study has shown that by determination of MBC and calculation of BR it is possible to reveal a certain degree of ventilatory insufficiency in symptom-free asthmatic children as a group. The errors of the method are, however, so great that it does not appear suited for evaluation of the pulmonary function in individual cases of symptom-free asthmatic children. A study of the single breath and of the mechanics of breathing should offer better possibilities for this purpose.

Summary

1. Maximal breathing capacity (MBC) and resting minute volume ($\dot{V}$) have been studied in 46 healthy children in the ages 7–14 years, 24 boys and 22 girls, and in 19 symptom-free asthmatic children in the same age range, 16 boys and 3 girls.

2. A correlation to body height was found in MBC but not in resting minute volume.

3. No significant correlation to body height was found in the calculated breathing reserve $[(MBC - \dot{V})/MBC] \times 100$, the mean value of which was 90.0 per cent in healthy children, corresponding closely to the figures found in earlier studies of children and adults.

4. The symptom-free asthmatic children showed as a group a significantly decreased maximal breathing capacity and breathing reserve, indicating a slight ventilatory insufficiency.

5. The value of this test in evaluation of ventilatory difficulties in individual cases is discussed.

Etude de la respiration chez l'enfant.
V. Ventilation maxima minute chez l'enfant normal et chez l'enfant asthmatique, sans symptôme respiratoire.

La ventilation maxima minute (MBC) et la ventilation minute au repos ont été étudiées chez 46 enfants normaux (24 garçons et 22 filles) âgés de 7 à 14 ans et chez 19 enfants asthmatiques (16 garçons et 3 filles) du même âge, sans symptôme respiratoire. Il existe une relation entre la taille et la ventilation maxima minute; mais non, entre la taille et la ventilation minute au repos. Aucune corrélation significative n'a été

trouvée entre la réserve de ventilation, calculée selon l'équation $[(MBC - \dot{V})/MBC] \times \times 100$, et la taille. La valeur moyenne de la réserve de ventilation atteint 90% chez les enfants normaux : ces valeurs confirment les résultats d'études antérieures. Le groupe des enfants asthmatiques, sans symptôme respiratoire, montre une diminution significative de la ventilation maxima minute et de la réserve de ventilation : signe d'une légère insuffisance ventilatoire. La valeur de ce test, utilisé pour évaluer une insuffisance respiratoire dans chaque cas particulier, est discutée.

Atmungsstudien bei Kindern.
V. Maximale Atemkapazität in gesunden Kindern und in symptomfreien Asthmakindern im Alter 7–14 Jahren.

Die maximale Atemkapazität (maximal breathing capacity, MBC) und das Ruhe-Minutenvolumen ($\dot{V}$) wurden bei 46 gesunden Kindern im Alter von 7–14 Jahren, 24 Jungen und 22 Mädchen, sowie bei 19 symptomfreien Asthmakindern derselben Altersgruppe, 16 Jungen und 3 Mädchen, bestimmt. Für die maximale Atemkapazität wurde eine Korrelation zur Höhe gefunden, nicht jedoch für das Ruhe-Minutenvolumen. Für die berechnete Atemreserve $[(MBC - \dot{V})/MBC] \times 100$ wurde keine signifikante Korrelation zur Höhe gefunden. Die Atemreserve ist durchsnittlich 90% von derjenigen bei gesunden Kindern, was durchaus den Werten entspricht, die bei früheren Untersuchungen in Kindern und Erwachsenen gefunden wurden. Die symptomfreien Asthmakindern zeigen als geschlossene Gruppe eine significante Minderung des MBC und des Ruhe-Minutenvolumens, was als Audruck einer leichten respiratorischen Insuffizienz angesehen werden muss. Die Wert dieses Tests für die Beurteilung der Ventilation in Einzelfällen wird erörtert.

Estudio de la respiración en la infancia.
V. Capacidad respiratoria máxima en el niño normal y en el niño asmático sin síntomas respiratorios.

La capacidad máxima respiratoria (MBC) y el volumen minuto en el reposo ($\dot{V}$) han sido estudiados en 46 niños normales (24 varones y 22 niñas) entre los 7 y 14 años de edad, y en 19 niños asmáticos (16 varones y 3 niñas) de la misedad, sin síntomas respiratorios. Se ha hallado una relación entre la talla y la capacidad respiratoria máxima pero no entre talla y volumen respiratorio minuto en reposo. Ninguna correlación significativa ha sido hallada entre la reserva ventilatoria calculada según la ecuación $[(MBC - V)/MBC] \times 100$ y la talla. El valor medio de la reserva ventilatoria alcanza 90% en los niños normales: estos valores confirman los resultados de estudios anteriores en niños y adultos. Los niños asmáticos sin sintomatología respiratoria muestran como grupo una significativa disminución de la capacidad respiratoria máxima y de la reserva ventilatoria indicando una ligera insuficiencia respiratoria. Es discutido el valor de esta prueba, utilizada en la valoración de una insuficiencia respiratoria en cada caso particular.

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PROGRESS IN PEDIATRICS

Primary (Genuine) Vitamin D Resistant Rickets

IV. A Clinical and Genetic Study[1]

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Owing to the rapid fall in the incidence of vitamin D deficiency rickets in many countries, increasing attention has been devoted to those types of rickets that appear in spite of adequate vitamin D prophylaxis.

Among various, etiologically different types of rickets which do not respond to usual vitamin D treatment, primary vitamin D resistant rickets constitutes a clinically well-defined entity. Since 1937, when the disorder was for the first time described in detail by Albright, Butler & Bloomberg, some hundred cases have been reported and the symptomatology and course of the disease have been fairly thoroughly studied. Detailed surveys have been published recently by Swoboda, and by Tobler, Prader & Taillard. The disease seems to be genetically determined; a dominant mode of inheritance has been observed repeatedly (Carlgren; Imerslund; Pedersen & McCarroll; Swoboda; Tobler *et al.*; Mitchell & Mitchell; Taillard, Tobler & Prader; Fanconi & Giradet; Christensen; Harrison; Dent & Harris). However, the incidence of isolated cases is fairly high. The pathogenesis of the disorder is still rather uncertain. Since the disease biochemically is characterized by a low serum phosphate level and a high urinary phosphate clearance (Fanconi *et al.*; Rupp & Swoboda; Zetterström & Winberg), it has been suggested that it develops as a consequence of an abnormally high urinary output of phosphate. Fanconi *et al.* have used the term phosphate diabetes, thereby implying that the pathogenetical basis of the disease may be a renal tubular dysfunction.

[1] The investigation was carried out with the aid of a grant from the Swedish Medical Research Council.

[2] We are highly indebted to Professor Torsten Sjögren, M.D., Head of the Psychiatric Clinic, for working facilities in his laboratory.

In this communication a methodical study of the clinical findings and of the mode of inheritance of primary vitamin D resistant rickets will be reported. The results, which are based upon the clinical examination of most known Swedish cases of this disorder and of their relatives, have provided material not only for a clinical and genetic analysis but also for a discussion concerning the criteria for the diagnosis of primary vitamin D resistant rickets and of the pathogenesis of the disease.

Material and Methods

Collection of the material.—The probands were obtained by an enquiry to the chief physicians at the children's hospitals in Sweden in 1955. A search of the records at the Orthopedic Clinic of Karolinska Institutet brought no fresh cases to light. It is a striking fact that not a single case of the disease was found in the northern part of Sweden (Fig. 1). Of course, this does not necessarily mean that the disease does not occur in this district; for various reasons, many cases, particularly those with mild symptoms, may have been overlooked.

Criteria for the diagnosis.—The criteria for the diagnosis of manifest primary vitamin D resistant rickets were as follows:

(*a*) The occurrence of skeletal changes resembling those found in rickets, in spite of adequate rickets prophylaxis or therapy.

(*b*) On some occasions a decreased serum phosphate level, together with a normal or subnormal calcium concentration, in association with a high serum alkaline phosphatase activity.

(*c*) The absence of such disorders which may be associated with or complicated by rickets resistant to vitamin D.

The cases classified as subclinical ones have presented slight leg deformities or abnormal skeletal structure on X-ray investigation. In all these patients the serum alkaline phosphatase activity has been increased (see Tables 1 and 2). The cases of suspected subclinical affection had only mild, if any, skeletal deformities, but the serum alkaline phosphatase activity was slightly above the upper normal limit.

Material.—Altogether there were 19 probands and 8 secondary clinically affected cases, these 27 patients representing 14 families (Table 1). Seven of the probands had been admitted to either the Norrtull Children's Hospital or the Pediatric Clinic of Karolinska Sjukhuset. Of these 7 patients, one has been described by Wallgren (Case 11a), and 2 by Winberg *et al.* (Cases 7a and 9a), while another 2 have been included in a study of the skeletal changes in primary vitamin D resistant rickets (Cases 5a and 14a) (Engfeldt, Zetterström & Winberg). Seven of the probands had been treated at the Pediatric Clinic in Falköping. The children of Family 3 had been admitted to the Princess Louisa Children's Hospital (Kronprinsessan Lovisas Barnsjukhus); one of these has been described by Carlgren and the whole family is reported by Christianson. Three probands had been admitted to the Pediatric Clinic in Lund; one of them (Case 8a) has been described by Englesson. One proband had been examined at the Pediatric Clinic in Halmstad.

Table 1 also includes 4 cases designated as subclinical, and 4 with probable subclinical manifestation; all 8 were secondary cases. Three of the probands (Cases 1b,

TABLE 1

Survey of the affected cases: clinically and subclinically affected.

Case no.	Proband (P) Secondary case (S)	Sex M = Male F = Female	Year of birth	Age at onset (yrs.)	Age on diagnosis (yrs.)	Age at disappearance from observation (years) Alive	Dead	Initial symptoms	Rickets prophylaxis	Maintenance dose of vitamin D[a]	Serum P mg %	Serum Alk. phosphatase	Clin. aff. (C) Subclin. (S)	Other "metabolic" disorders
1 a	P	M	1948	1 8/12	2 2/12	9		Retarded physical development	+	Moderate	6.2	20	C + +	0
1 b	P	F	1954	–	3/12	3		Cf. text	+	High	–	–	C + +	0
1 c	S	F	1946	–	10	10		Slightly curved legs	+	0	6.2	27.5	C +	0
1 Aa	S	M	1917	?2–3	35	40		Bow-legged	Unknown	0	4.9	13.5	C + +	0
1 Ba	S	F	1887	–	–	–	37	Bow-legged	Unknown	0	–	–	C + +	x[c]
2 a	P	F	1950	1 2/12	1 5/12	6		Bow-legged	+	High	7.2	27	C + +	0
2 b	P	F	1953	–	6/12	4		Cf. text	+	High	7.2	22	C + +	0
2 c	P	M	1955	–	2/12	1 1/2		Cf. text	+	High	7.4	51	C + +	0
2 Aa	S	M	1919	?2–3	33	38		Bow-legged	Unknown	0	5.2	14	C + +	0
2 Ba[d]	S	F	1887	–	–	–	37	Bow-legged	Unknown	0	–	–	C + +	x
3 a	P	Case 3 a and 3 Aa published by Carlgren, 1948. A report of the whole family has been given by Christiansson 1958. The family is included in the genetic analysis only.												
3 b	P													
3 c	S													
3 Aa	S													
4 a	P	M	1948	1–2	2–3	9		Bow-legged	+	Moderate	3.5	45	C + +	0
4 Aa	S	F	1919	?1–2	32	38		Bow-legged	Unknown	0	2.8	8	C + +	0
5 a	P	F	1952	1 1/2	3	5		Could not learn to walk. Curved legs	+	Extremely high	4.6	78	C + + +	0
5 b	S	M	1955	–	11/12	1 10/12		[b]	+	Moderate	3.6	65	C + +	x
5 Aa	S	F	1917	–	39	40		Slightly curved legs	Unknown	0	4.0	11.5	S	0
5 c	S	F	1943	–	13	14		Slightly curved legs	+	0	5.8	25	?S	x
5 d	S	M	1946	–	10	11		0	+	0	6.1	30	S	0
7 a	P	M	1948	1 3/12	2	8 1/2		Curved legs	–	High	7.4	16	C + + +	alopecia prolinuria

5 Aa	S	F	1917	–	39	40	Slightly curved legs	Unknown	0	4.0	11.5	S	x
5 c	S	F	1943	–	13	14	Slightly curved legs	+	0	5.8	25	?S	x
5 d	S	M	1946	–	10	11	0	+	0	6.1	30	S	0
7 a	P	M	1948	$1\frac{3}{12}$	2	$8\frac{1}{2}$	Curved legs	–	High	7.4	16	C+++	alopecia prolinuria
7 Aa	S	M	1912	–	44	45	0	Unknown	0	3.2	12	S	x
7 b	S	F	1942	–	14	15	0	?+	0	4.0	30	?S	x
8 a	P	M	1946	$\frac{8}{12}$	2	11	Metaphyseal enlargement	+	Extremely high	6.3	39.5	C+++	Hydroxyprolinuria
8 b	P	F	1947	$1\frac{1}{12}$	$1\frac{1}{12}$	$9\frac{1}{2}$	Could not learn to stand	+	Extremely high	6.0	22	C++	0
9 a	P	M	1945	$1\frac{8}{12}$	3–4	$11\frac{1}{2}$	Thick wrists and foot joints	+	High	7.0	30	C+++	albinism
9 b	S	M	1938	–	18	19	0	?+	0	6.6	21	S	x
10 a	P	F	1944	$1\frac{2}{12}$	10	13	Bow-legged	+	Moderate	3.6	48	C++	0
10 b	S	F	1952	–	4	$4\frac{1}{2}$	0	+	Moderate	7.0	25	?S	x
11 a	P	M	1948	$1\frac{3}{12}$	2	9	Could not learn to walk	(+)	High	6.7	37	C+++	0
12 a	P	F	1947	$1\frac{1}{2}$	2–3	10	Curved legs, limped	+	Moderate	5	28	C++	x
13 a	P	F	1945	$1\frac{1}{2}$	9	12	Bow-legged	–	High	3.4	45	C++	0
14 a	P	F	1951	1	3	6	Bow-legged	+	High	3.2	40	C++	0

[a] Moderate = < 1000 units/day. Rather high = 1000–5000 units/day. High = 5000–50,000 units/day. Extremely high = > 50,000 units/day.

[b] Diagnosed at the field investigation. Marked changes in serum chemistry and typical X-ray findings, although physical examination had revealed normal skeleton.

[c] x = not tested for amino aciduria by paper chromatography.

[d] This is the same case as 1Ba.

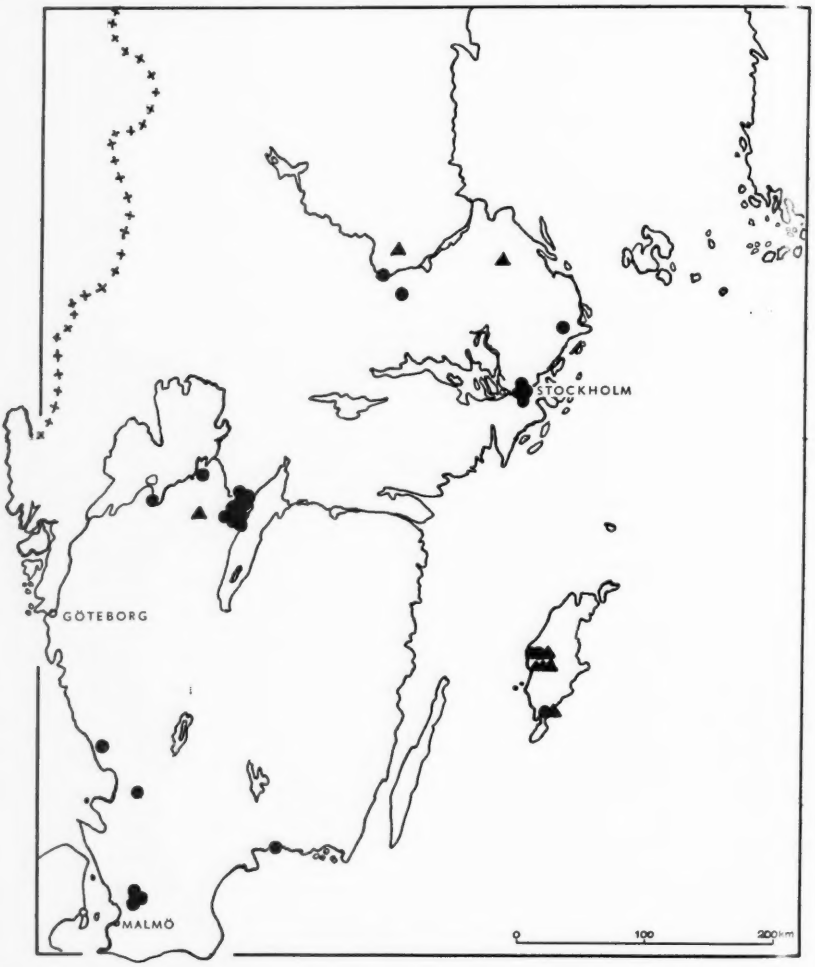

Fig. 1. The birthplaces of the affected cases. ● = clinically affected; ▲ = subclinically affected.

2b and 2c) were diagnosed at a very early age, most likely because they had affected siblings.

Clinical and laboratory investigations.—In 1956 as many as possible of the probands and their closest living relatives were examined clinically by one of the authors (K. L.) during a field investigation. Particular attention was given to the presence of skeletal deformities and such other abnormalities as might be attributable to metabolic disorders. In some questionable cases X-ray investigation of the skeleton was performed. At the same time as the physical examination was performed, venous blood was drawn

TABLE 2

Variation of serum alkaline phosphatase activity with age in healthy children.

Sex M = male F = female	Age (years)	Number of cases	Range (units/100 ml)	Average value (units/100 ml)
M	> 20	11	6–10	7.2
M	19–20	3	6–9	7.0
M	17–18	–	–	–
M	15–16	5	17–25	20.4
M	13–14	12	10–34	21.0
M	10–12	12	12–23	18.4
F	> 20	5	3–7	5.2
F	18–20	–	–	–
F	15–17	6	8–12	9.5
F	13–14	9	6–26	15.1
F	10–12	14	14–26	20.4
M + F	0–9	22	6–20	13.9

for the estimation of the serum levels of inorganic phosphate (according to Youngberg & Youngberg) and calcium (according to Biering), and the alkaline phosphatase activity of serum (according to Buch & Buch). In the clinically affected cases the urinary amino-acid excretion was determined as described by Dent; the creatinine concentration was used as a reference. Blood-group determinations were performed to ascertain whether there was any genetic linkage.[1]

As an increase in the alkaline phosphatase activity in the serum was regarded as a possible indication of subclinical manifestation of the disease, it was considered necessary to make a study of the normal range of activity at various ages for Swedish children. The results of this study are presented in Table 2. The values agree with those reported by H. Buch for Danish children. The case series is too small for statistical analysis, but it is evident that the phosphatase activity varies widely according to age, being highest during periods of rapid growth. Since there are large individual variations for the time when pubescence starts, the range for alkaline phosphatase activity is extremely wide for the ages of 11–16 years.

Clinical Analysis

Age at onset and at diagnosis

As far as it was possible to establish these data they are given in Table 1. In most of the probands the initial symptoms—mainly deformities of the lower extremities and inability to learn to walk—were observed during their second year of life. That the disease may be manifested much earlier than

[1] The serologic work has been performed at the National Rh Laboratory under the guidance Prof. B. Broman.

during the second year of life is, however, evident from the fact that in 4 cases the diagnosis was made at the ages of 2, 3, 6 and 11 months, respectively. In these cases the diagnosis was made on the basis of roentgenological findings or biochemical abnormalities such as markedly elevated serum alkaline phosphatase activity in association with moderately low serum phosphate concentration. Even at such early ages the physical examination may show definite skeletal abnormalities, such as coxa vara and some shortening of the lower extremities. The appearance of the infants was reminiscent of chondrodystrophic dwarfism (Cases 1b and 2c). The very early onset in Cases 1b and 2c suggests a fetal onset of the disease which is not in accord with previous observations and the designation of the disorder as "late rickets" (see Tobler *et al.*). In instances without any symptoms during early childhood, the clinical onset may coincide with the accelerated growth prior to adolescence. This suggestion is supported by the findings in Case 1c (a secondary case). Examination of this patient revealed an increased alkaline phosphatase activity and X-ray investigation of the skeleton disclosed mild but typical changes. Still milder cases than this may fail to present any clinical symptoms.

The disease was generally diagnosed soon after the clinical onset. In some patients where the recognition was delayed the condition had at first been regarded as vitamin deficiency rickets, or as sequelae of this disease. A few of these patients were treated orthopedically, but, because of reappearance of the leg deformities, the diagnosis was reconsidered.

Clinical symptoms

In all affected patients above 18 months old the legs were more or less deformed; which is in agreement with other observations (Pedersen & McCarroll; Swoboda; Tobler *et al.*). In severe cases these deformities were so marked that the patients were unable to walk (Case 9a). Many patients exhibited pronounced coxa vara. Deformities of the arms, the thorax or the trunk were rather rare and marked changes were only found in a few severe cases with an early clinical onset (Cases 5a, 6a, 8a, and 9a). However, wrist enlargement was rather common. In a few cases the head was abnormal in shape (dolichocephaly and caput quadratum). Only two patients presented symptoms suggestive of other metabolic disturbance; Case 9a had albinism and Case 7a a total alopecia.

Laboratory findings

X-ray examination of the skeleton showed typical changes of varying degrees of severity, such changes being present even at such an early age

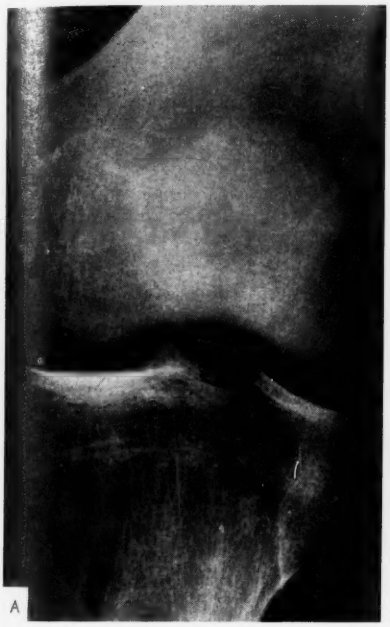

Fig. 2. Roentgenograms from three members of the related Families 1 and 2.

A. From the knee, case 2Aa at an age of 21 years. As can be seen there are no signs of active rachitic process, but there is a typical coarse trabecular structure. In this patient there were marked deformities and the alkaline phosphatase activity in serum was rather high. No therapy at present time. Although the roentgenogram does not show any signs of active rickets, the presence of abnormal structure and high serum alkaline phosphatase activity suggests that the process is still active.

B. From the wrist of case 2c at an age of 7 weeks. The patient is the son of case 2Aa whose roentgenogram is shown in *A*. There are marked changes typical of rickets in the distal part of radius and ulna. The presence of these severe changes at such an early age is very likely consistent with the view that the skeletal disorder has started during fetal life.

C. From the knee of case 1c at an age of 11 years. This child, who had never shown any signs of rickets, was, when investigated, found to have a high alkaline phosphatase activity in serum, although there were no marked deformities. The roentgenogram clearly shows active rickets.

Fig. 3. Roentgenogram of the wrists from two members of Family 7.

A. The proband case 7a at an age of almost 3 years. The roentgenogram was taken before treatment was started. Typical changes are clearly seen.

B. Subclinical case 7Aa at an age of 45 years. This case is the father of the patient whose roentgenogram is shown in *A*. There were no deformities but the serum alkaline phosphatase activity was rather high. The skeletal structure is coarse trabecular and resembles that of case 2Aa (Fig. 2*A*).

as 2 months, the characteristics being the same as those described by Fairbank, and by others. In questionable cases roentgenological examination proved to be of great value. The X-ray findings in typical cases and in those with subclinical manifestations are shown in Figs. 2–4. Studies of the serum chemistry revealed varying results due to variability of the severity of the disease and due to the lack of therapeutic uniformity. In all patients the serum calcium level was found to be normal. In several instances, the serum phosphate level was low (Table 1). As is also shown in Table 1 the concentration was, however, normal in a number of treated cases, in spite of the fact that the disease process was still going on, as reflected in increased alkaline phosphatase activity. This is not in agreement with the statement made by Tobler *et al.* who consider that the serum phosphate level is regularly decreased in primary vitamin D resistant rickets, even after adequate treatment and normalization in other respects. The finding that the alkaline phosphatase activity was increased in several patients, who otherwise exhibited normal biochemical findings, is in accordance with the suggestion that

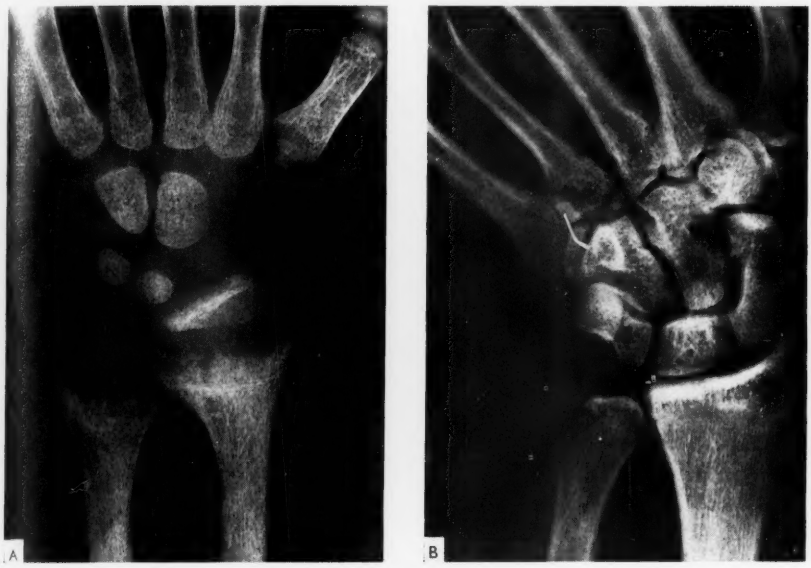

Fig. 4. Roentgenogram of the wrists from two members of Family 9.

A. The proband case 9a at an age of 6 years, before therapy was started. There are severe changes typical of rickets.

B. Subclinical case 9b, a brother to case 9a, at an age of 19 years. He was quite healthy and there were no deformities, but the serum alkaline phosphatase activity was rather high. The roentgenogram shows the same changes as those demonstrated in Fig. 2*A*.

estimation of the alkaline phosphatase activity of serum may serve as a useful guide in the control of patients with primary vitamin D resistant rickets (Zetterström & Winberg).

The urinary output of amino acids was investigated in several patients (Table 1). In none of the patients was there a real amino aciduria of the type which develops in vitamin-deficiency rickets (Jonxis, Smith & Huisman). However, one patient (Case 7a) had a high excretion of proline and another of hydroxyproline (Case 8a). The significance of these findings in two patients is difficult to assess. No patient exhibited glycosuria.

Therapy, course and prognosis

The severity of the disease varied widely, and hence also its course. As is seen from Table 1 the maintenance dose of vitamin D differs widely from one patient to another. It is, however, impossible to decide whether the dose was the optimal one in all cases.

A comparison between the various age groups as regards physical findings and the results of the laboratory investigations shows that the disease is progressing during periods of rapid growth. After growth has ceased there is an apparent recovery, although the laboratory investigations also in adult patients may reveal evidence of activity of the disease process (increase in the serum alkaline phosphatase activity). Despite deformities of the legs, the physical capacity for work is not appreciably reduced in our adult patients. The course of primary vitamin D resistant rickets thus is quite different from that in vitamin D resistant osteomalacia, which does not appear until adult ages, and then usually progresses successively (Dent & Harris).

The course of the disease varied somewhat from one family to another. In Families 1 and 2, which were consanguineously related, the deformities of the lower extremities and the appearance of coxa vara were the most pronounced features of the clinical picture. In Families 5 and 6, also related, and where the mode of inheritance also appeared to be dominant, the manifestations of the disease in the primary cases were appreciably more pronounced than in Families 1 and 2. However, in both these families, the mothers, who were sisters, were very mildly affected and were designated as subclinical cases. The solitary cases were affected to varying degrees. There was no difference between these patients and cases with an established dominant mode of inheritance. The changes of the serum chemistry also differed somewhat from one family to another. All patients in the related Families 1 and 2 had a normal serum phosphate level during the course of therapy, while the alkaline phosphatase activity was high. In other families the phosphate was low in addition.

Genetic Analysis

The analysis was based on the 27 clinically and the 8 subclinically affected cases distributed among 14 families. Families 1 and 2 were consanguineously related, as were Families 5 and 6. The genealogical research in the parish registers and archives covered a total of 452 persons (siblings, parents, parental siblings and grandparents). In most of the familial cases the disorder is very probably due to a single dominant gene mutation. Moreover, the place of birth of the affected and their parents in the various families, with the exception of Nos. 1, 2, 5 and 6, were distributed throughout the country. For this reason the genealogical research with regard to distant ancestors was centred on the ancestral lines that were suspected of converging. A survey of the traced ancestors is given as Table 3. The geographic distribution of the cases of primary vitamin D resistant rickets according to place of birth is shown in Fig. 1.

TABLE 3

Survey of traced ancestors.

Family	Generation II	III	IV	V	VI	VII	Total number of ancestors traced
1	2	4	8	6	–	–	20
1 A	2	4	4	–	–	–	10
1 B	2	4	–	–	–	–	6
2	2	4	8	6	–	–	20
2 A = 1 A							
3	2	4	3	4	–	–	13
3 A	2	3	4	–	–	–	9
4	2	4	8	16	12	–	42
4 A	2	4	8	12	–	–	26
5	2	4	7	14	4	6	37
5 A	2	4	8	2	4	–	20
6	2	4	8	8	2	4	28
6 A = 5 A							
7	2	4	7	2	–	–	15
7 A	2	4	–	–	–	–	6
8	2	4	7	10	1	–	24
9	2	4	8	2	4	–	20
10	2	4	8	14	24	–	52
11	2	4	8	6	6	–	26
12	2	4	6	9	2	–	23
13	2	4	8	10	2	–	26
14	2	4	8	–	–	–	14
Total	40	79	127	115	49	10	340[a]

[a] Common ancestors are counted once only.

Analysis of the individual families

A survey of the series is given in Tables 1 and 4. Of the 14 families, 7 (10, if the subclinically affected are included) presented a familial occurrence of the disease. In 4 families (Nos. 1–4) one of the parents suffered from manifest rickets, in 2 families (Nos. 5 and 7) one of the parents was designated as subclinically affected, and in one family (No. 6) subclinical affection of one of the parents was suspected. In 2 families that were related (Fig. 5) the disease was encountered in at least 3, and probably more, generations, since it was known in the district that there had been a skeletal disease in the family for generations. Primary vitamin D resistant rickets being a rare disorder, the pedigrees provide convincing evidence that it has its causation in a single dominant gene in Families 1–4. The inheritance

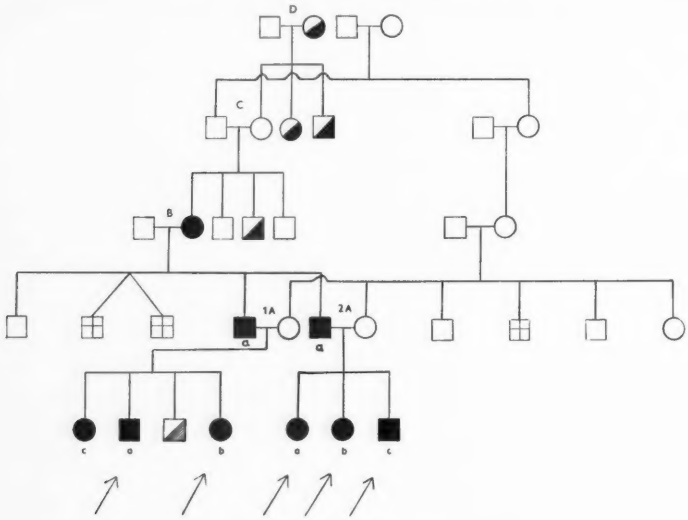

Fig. 5. Pedigree chart: Families 1 and 2.

■ = primary vitamin D resistant rickets, clinically affected.

◪ = primary vitamin D resistant rickets, uncertain case (diagnosis based on case history).

⊞ = died in infancy.

▨ = mild ordinary rickets at the age of one year.

↗ = indicates proband.

is very probably dominant also in Families 5 and 6, where the probands are first cousins (Fig. 6), and in Family 7, where the subclinically affected father presented roentgenological skeletal changes. In no family were secondary cases met with in both parental lines.

The mothers of Families 5 and 6 may be regarded as carriers of the gene, since they are sisters. The fact that one of them was designated as subclinically affected and the other was suspected of being subclinically affected thus suggests that the persons who were not clinically affected, though evidencing activity, should be regarded as affected.

It is of interest to note that affected grandparents were encountered in only 2 families, which were related (Fig. 5). This is, however, consistent with the hypothesis of the disorder being due to a single dominant gene in any of the following conditions: (1) Some cases escaped diagnosis. (2) The affected parents of probands represent new mutations. (3) The penetration is incomplete.

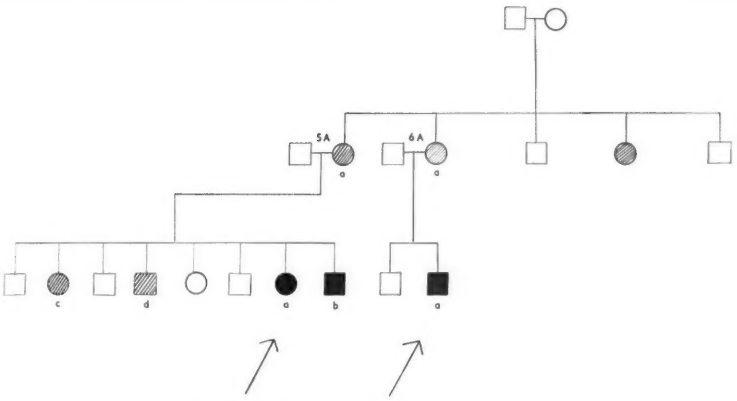

Fig. 6. Pedigree chart: Families 5 and 6.

■ = primary vitamin D resistant rickets, clinically affected.

▨ = primary vitamin D resistant rickets, subclinical case.

↗ = indicates probands.

These conditions are considered in turn:

(1) The grandparents of the probands were not examined. It is therefore probable that some cases that were in fact affected were overlooked, especially where the condition was clinically mild, or subclinical.

(2) This possibility is discussed below.

(3) In this connection it should be mentioned that the degree of penetration for a disease must be judged in the light of the criteria according to which the diagnosis is made, and thus also in relation to the methods of investigation. Support for the hypothesis of incomplete penetration is found if the disease skips a generation. As regards primary vitamin D resistant rickets, however, no instance of this has, as far as we are aware, been reported in the literature. Nor was any skipping found in the present case series, unless the subclinically affected mothers of Families 5 and 6, regarded as carriers of the gene, are presumed to be unaffected. Incomplete penetration is, however, *a priori* probable in primary vitamin D resistant rickets, where the expressivity is particularly variable. Thus, of a single family one or more members could be severely affected by the disease, while other members presented only roentgenological changes and abnormalities of the serum chemistry.

The analysis of the importance of genetic factors is more complicated in the other 7 families (Nos. 8–14), where no signs of affection could be found in any of the parents; 7 of the probands were solitary cases with regard to

the clinically manifest condition. The possibility exists that for these patients, the disorder had its origin in exogenous factors. However, no such factors could be demonstrated. Nor did these patients differ in clinical respects from those having affected parents. The occurrence of the solitary cases and of the two cases in Family 8 is fully consistent with a hereditary origin on any of the following conditions: (1) The disorder is due to a single dominant gene, but the penetration is incomplete. (2) The disorder is not due to a single dominant gene. (3) The solitary cases represent fresh mutations. (4) Some secondary cases escaped diagnosis.

These conditions are considered in turn:

(1) As mentioned earlier, no reliable evidence of a single dominant gene with incomplete penetration was adduced, although this possibility is not *a priori* improbable.

(2) In the case of rare recessive conditions a parent is almost never affected. Moreover, one may expect a high rate of consanguineous marriages among the parents of the affected. In our case series the parents are related in 4 of the 14 families. In one case (Family 7) there is a first-cousin marriage, the parents also being related 3:3. In a further 3 families (Nos. 1, 2 and 11) the parents are related 3:3. Since the series is so small, no reliable conclusion as regards recessivity may be drawn from the high proportion of marriages between related parents. It is clear, however, that in two cases (Families 1 and 2) the consanguinity was of no significance, since here the disease presents a typical dominant inheritance, all the cases in the ancestral line being traceable to the affected parent. In Family 7, too, the inheritance is probably dominant. There was thus no reliable evidence of recessive inheritance.

In view of the varying expressivity, a multifactorial inheritance is conceivable, though impossible to establish.

(3) Man can be looked upon as a wild population inasmuch as he is subject to the influence of natural selection. Genes that give rise to diseases manifested in early life tend to be eliminated owing to a reduced effective fertility. If this tendency is not offset by fresh mutations, dominant hereditary diseases rapidly disappear from the population. In human genetics hereditary diseases are generally assumed to be balanced; that is to say, equilibrium is considered to exist between various selective factors.

As regards primary vitamin D resistant rickets it may be assumed *a priori* that the physically deformed, clinically affected persons are less likely to marry than healthy people, and that the effective fertility is thus reduced. However, no confirmation of this assumption was possible in this material, in which all the clinically affected adults are married parents of probands. The average number of children born to affected parents—3.2 if only clinically affected parents are counted, 3.6 if subclinically affected are

included—is not particularly low, but it must be borne in mind that the case series is small. It is definitely too small to permit a reliable determination of the mortality. However, only one case of still birth (a boy in Family 5 A) and 5 deaths in infancy (one pair of twins in Family 1 A = 2 A, and a maternal uncle in each of Families 1, 2 and 3) were encountered. The incidence of stillbirths and the infant mortality rate among the 69 siblings of the probands and of the clinically and subclinically affected parents are not significantly higher than the corresponding rates in the general Swedish population.

As neither the fertility in primary vitamin D resistant rickets nor the incidence of the disease in the general population can be calculated, the mutation rate cannot be found. It is not improbable, however, that one or more of the solitary cases originated in a new mutation of a dominant gene.

(4) All living parents and siblings of probands with the exception of 4 cases (2 parents and 2 siblings) were physically examined by one of the authors; and in all but 3 of them the serum chemistry was investigated. It is probable that all clinically fully developed cases of primary vitamin D resistant rickets in these classes of relationship were diagnosed, whereas one or more of the subclinical cases may have been overlooked. Among the siblings of parents and the grandparents, who were not systematically examined, some cases were probably overlooked.

It is possible that the mother of Family 8, who presented marked symptoms of rickets as a child, was in fact a case of primary vitamin D resistant rickets. In this instance, however, there was no sign of activity, and for this reason no definite diagnosis can be made.

Sex distribution

Primary vitamin D resistant rickets is inherited by both sons and daughters from the father and the mother. The sex distribution reveals no noteworthy features. In the proband generation and among the affected parents and their siblings 12 out of 33 males and 14 out of 32 females were clinically affected, with respectively 3 and 5 subclinically affected (Table 4). Here and below, no distinction is made between definitely and probably subclinically affected individuals. The fact that the children of an affected father and an unaffected mother are of either sex constitutes evidence against sex-linked dominance, whether partial or total. Any possibility of crossing over is here disregarded.

TABLE 4

Survey of the families.[a]

Family number	No. of affected Clin. □	Clin. ○	Subclin. □	Subclin. ○	Number of unaffected siblings[b] M	F	Consanguinity between the parents	Other diseases among parents F = Father M = Mother	Other diseases among siblings B = Brother S = Sister
1	1	2	–	–	1	–	3 : 3	–	B: mild ordinary rickets at the age of one year
1 A	2	–	–	–	1	–	–	–	–
2	1	2	–	–	–	–	3 : 3	–	–
2 A = 1 A	2	–	–	–	1	–	–	–	–
3	1	2	–	–	–	–	–	This pedigree has been published by Christiansson	
3 A	–	1	–	–	1	1	–		
4	1	–	–	–	–	–	–	–	–
4 A	–	1	–	–	–	1	–	F: died of tuberculosis M: short stature	–
5	1	1	1	1	3	1	–	–	–
5 A	–	–	–	2	2	1	–	M: short stature	B: died aged 2; cause unknown S: "funny legs"
6	1	–	–	–	1	–	–	–	–
6 A = 5 A	–	–	–	2	2	1	–	M: short stature	B: died aged 2: cause unknown S: "funny legs"
7	1	–	–	1	1	–	2 : 2; 3 : 3	–	–
7 A	–	–	1	–	3	3	2 : 2	M: cancer	BSS: died of pulmonary tuberculosis in adult age
8	1	1	–	–	1	2	–	M: rickets	B: died in an accident aged 12
9	1	–	1	–	1	1	–	–	S: died of appendicitis aged 5
10	–	1	–	1	–	1	–	–	–
11	1	–	–	–	2	1	3 : 3	M: otosclerosis	–
12	–	1	–	–	–	–	–	–	–
13	–	1	–	–	–	–	–	–	–
14	–	1	–	–	1	1	–	–	B: eczema

[a] Family 1 B (= 2 B) is not included, owing to insufficient data on siblings.
[b] Stillborn children and those who died in infancy are not included.

TABLE 5

Birth rank of the affected children.

Size of sibship	No. of families	No. of affected children	Birth rank of affected children 1	2	3	4	5	6	7	8
		Clinically affected								
1	3	3	3							
2	2	2	1	1						
3	7	12	5	4	3					
4	3	5	1	1	–	3				
5	1	2	–	–	–	1	1			
6	–	–	–	–	–	–	–	–		
7	–	–	–	–	–	–	–	–	–	
8	1	2	–	–	–	–	–	–	1	1
Total	17	26								
		Clinically + subclinically affected								
1	3	3	3							
2	2	2	1	1						
3	7	14	5	5	4					
4	3	6	2	1	–	3				
5	2	4	1	1	–	1	1			
6	–	–	–	–	–	–	–	–		
7	1	1	–	–	1	–	–	–	–	
8	1	4	–	1	–	1	–	–	1	1
Total	19	34								

Birth rank

The birth rank of the affected is shown in Table 5. The observed distribution does not differ from a random distribution. Of the clinically affected, 10 belong to the earlier half of the sibship and 13 to the later half; 7 are eldest children and 9 youngest. If subclinically affected are counted, 16.5 lie in the earlier and 14.5 in the later half; 9 are eldest and 10 youngest children. In the analysis one-child families have been excluded, since they provide no information.

Morbidity rate for primary vitamin D resistant rickets among siblings and parents of probands

Primary vitamin D resistant rickets is evidently a very rare disease; only 26 cases have been diagnosed in children's hospitals in Sweden in recent years. All clinically affected siblings of probands were also probands, with the exception of one girl (Case 1 c) and one boy (Case 5 b), these cases being

diagnosed during the field investigation. In the case of the boy, who was 11 months old at the time of examination, the clinical symptoms had still not developed. It is very probable that this child would have been admitted to hospital when the symptoms became manifest. Hence, as regards the clinically manifest condition the ascertainment was almost complete.

The diagnosis of the eldest clinically affected proband in each family had in all cases been made before the other siblings presented the disease. This contradicts the assumption that the proband families represent a selection of families with many affected. Cases 1b, 2b and 2c were, however, diagnosed at the hospital when extremely young (Table 1) owing to the fact that their elder siblings were affected. They were thus registered as probands. On the other hand these cases developed clinical symptoms of the same severity as were presented by their elder affected siblings. It is therefore very likely that, irrespective of the fact that their siblings were primary cases, they would have been diagnosed, but at a somewhat higher age. It may be concluded that the material, although small, is sufficiently representative to permit a calculation of the morbidity rates among the siblings and parents. Moreover, during the field investigation the families (probands, siblings and parents) underwent physical and laboratory examinations.

The observed morbidity rate among the siblings of the probands is 17/44 (39 per cent) if only clinically affected are considered, and 22/44 (50 per cent) if the subclinical cases are included. In the analysis, account was taken of "experiences"; that is to say, each sibling was counted as many times as there were probands in the family; by excluding one proband from the calculation each time a family is counted, account is taken of the fact that the families were registered on the basis of one affected, that is, the proband (see Weinberg). The numbers of affected parents (experiences) are 8 out of a total of 38 (21 per cent) and 11 out of 38 (29 per cent), respectively.

A calculation of the morbidity rate among siblings of probands was also performed on the basis of the probably dominant families with parental mating *affected* × *unaffected* (Families 1–7, and 1A = 2A in which the affected parents were counted as probands). These families may be assumed to be more homogeneous from the genetic aspect. However, it is, of course, possible that we are concerned with genetically distinct but clinically similar diseases, originating in dominant mutations at different loci. The observed frequency of clinically affected siblings of probands is 17/30 (57 per cent), and 20/30 (67 per cent) if the subclinically affected siblings are included. The difference between the observed and expected frequency (50 per cent) in the case of the disorder being due to a single dominant gene is not statistically significant.

Calculation of the morbidity rate in Families 1–7 when only one affected

was chosen as a proband gave the proportion of clinically affected siblings as 7/17.

In the families of which none of the parents was affected (Families 8–14) the morbidity rate for the clinically affected siblings of probands is 2/18, and for the clinically and subclinically affected 4/18.

As the homogeneity of the series from the genetic aspect is uncertain, a more detailed statistical analysis was not performed.

Other morbid conditions in the families of the affected

One proband had alopecia and prolinuria, another had hydroxy-prolinuria, and a third albinism (Table 1). These metabolic disorders and primary vitamin D resistant rickets may well be different manifestations of the same gene. It is possible that these cases are genetically distinct from one another and from others, and had their origin in mutations at different loci, but they may also be a manifestation of pleiotropism. Otherwise the affected presented no associated disorders of interest. It should be pointed out that no case of severe mental disturbance was encountered.

Among the unaffected parents of the clinically and subclinically affected parents of the probands there were 2 cases of remarkably short stature, and among the unaffected siblings of the parents there was one person who was reported as having had peculiarly shaped legs (Table 4). These deviations may be symptoms of primary vitamin D resistant rickets, but no definite conclusions in this respect could be drawn from the available data. The possibility that in respect of the mother of Family 8 the condition diagnosed in childhood as rickets was in fact primary vitamin D resistant rickets has already been discussed. No other conditions of genetic interest were found among the unaffected relatives.

Study of linkage.—Studies of linkage are of practical as well as of theoretical interest since a knowledge of it enables carriers of the gene to be identified and the risk of affection to be predicted for a given member of the family, in which a hereditary disease occurs, who has not reached the age at which the condition usually becomes manifest.

For the study of linkage in the present study the occurrence of markers was recorded, those used in this connection being various blood-group antigens, and taste sensitivity to phenylthiocarbamide in a dilution of 5:100,000. The following blood-group systems were tested: A, B, O; M, N, S; Rh (Rh_1, Rh_2, rh). The number of cases accessible was unfortunately too small to warrant statistical analysis; the mode of inheritance was known with a satisfactory degree of certainty in only 7 families, one of which contained only one child. Moreover, some patients were not available for the tests. The data in the series was recorded and filed for use in subsequent studies when supplemented with new cases.

Discussion

The genetic analysis clearly indicated that, in several families, primary vitamin D resistant rickets is due to a single dominant gene. The inheritance in the other families could not be established with certainty.

Various interpretations are possible. A reduced penetration is not unlikely in view of the widely varying expressivity. In several of the families one of the parents presented a high serum alkaline phosphatase activity and a coarse trabecular structure at the skeletal X-ray; findings suggesting the presence of the disorder in spite of the absence of all except perhaps mild clinical symptoms (i.e. subclinical cases). This suggests that the diagnosis is not always plain and straightforward and that it may have been overlooked in some of the cases that were not thoroughly examined. The possibilities of a recessive and a multifactorial inheritance must be borne in mind, although there is no reliable evidence in favour of any of them. That one or more of the solitary cases had their origin in a dominant fresh mutation is not improbable.

The clinical and genetic analyses together provide clear evidence that the clinically unaffected cases that display activity should be considered as affected. Thus, subclinical cases that presented skeletal changes as evidenced from X-ray examination were found in families with severely affected members. It is interesting to note that in two families in which a dominant mode of inheritance was very likely, one of the mothers most probably carrying the gene, though clinically unaffected, presented increased serum alkaline phosphatase activity. Taillard *et al.* have recently made a similar observation. They found a pathologically-low serum phosphate level in a clinically unaffected woman who was probably a carrier.

It would be of value to establish a more reliable basis for the diagnosis of the condition. The mere occurrence of rickets is, of course, insufficient for a diagnosis of primary vitamin D resistant rickets in an adult. Evidence of activity, in spite of an apparent recovery, is probably required. The results of the investigation suggest that the alkaline phosphatase activity in the blood serum may serve as a guide in doubtful cases. Radiographs of the skeleton would in theory be of value (Fig. 4–6) (the occurrence of coarse trabecular structure), but such a method is probably too rough for the demonstration of only slight changes.

No difference was found between cases due to a single dominant gene and the solitary cases. There were no signs of pathogenetically distinct conditions. It was not possible to demonstrate any connection between resistant rickets and osteomalacia with onset at adult ages.

Some of the observations may elucidate the pathogenesis of primary

vitamin D resistant rickets. In some of the cases in Families 1 and 2 the alkaline phosphatase activity was increased, while the serum phosphate concentration was within normal ranges; that is to say, there were signs of activity in spite of a normal serum phosphate level. This finding is hardly consistent with the assumption that the primary cause of the disease is loss of phosphate via the urine due to a congenital renal tubular defect resulting in a decrease of the serum phosphate level. Observations made by Harrison on an infant of a mother having resistant rickets bears out this view. At birth the child had normal serum chemistry, but at the age of 7 months the alkaline phosphatase activity was very high, in spite of a practically normal serum phosphate concentration. The initial symptom in this patient was thus a marked rise in the serum alkaline phosphatase activity and only subsequently was a fall in the phosphate level evident.

Summary

1. A clinical and genetic study of primary vitamin D resistant rickets has been performed on the basis of 27 clinically affected cases distributed among 14 families, 7 of them being solitary cases. Eight secondary cases—parents and siblings of the probands—were designated as definitely or probably subclinically affected.

Those cases classified as subclinically affected exhibited a slightly increased serum alkaline phosphatase activity, slight deformities, and roentgenological skeletal changes. These features suggest a widely varying expressivity of the condition.

2. The onset of the disease seems to occur at varying ages, but usually in the second year, although definite clinical signs were demonstrated in very early infancy. In two cases there was strong evidence of a prenatal onset.

3. The serum alkaline phosphatase activity appears to serve as a useful guide where other signs of the disease are absent.

4. The genetic analysis clearly suggests that, in 4 families, the disease is due to a single dominant gene. The same is very probable of a further 3 families. In the other cases the etiology could not be established with certainty. Various genetic interpretations are discussed.

5. Although the material is small it is sufficiently representative to justify a calculation of the morbidity rate for the siblings of the probands. The observed rate for children with the parental mating affected × unaffected is consistent with the assumption of a single dominant gene mutation.

6. There was evidence that the disease may display a varying degree of manifestation in a particular family. There was no clinically demonstrable difference in the condition whether it presented familial or isolated occurrence.

7. The pathogenesis of primary vitamin D resistant rickets is briefly discussed.

Rachitisme primaire (véritable) resistant à la vitamine D. IV. Une étude clinique et génétique.

1. On a effectué une étude clinique et génétique du rachitisme primaire résistant à la vitamine D, en se basant sur 27 cas cliniques, répartis parmi 14 familles dont 7 étant des cas isolés. 8 cas secondaires — parents et frères et sœurs des malades eux-

mêmes — ont été désignés, sûrement ou probablement, comme atteints cliniquement d'une façon secondaire. Ces cas classés comme atteints cliniquement d'une façon secondaire démontrèrent une activité faiblement augmentée de la phosphatase alcaline du sérum, des déformations légères, et des modifications squelettiques radiologiques. Ces données font penser à une caractéristique largement variée de la maladie.

2. Le début de la maladie semble se manifester à des âges différents, mais en général dans la deuxième année, bien que des signes cliniques définitifs se montrèrent à un âge très bas. Dans deux cas, il y eut une forte preuve d'un début prénatal.

3. L'activité de la phosphatase alcaline du sérum semble servir comme un guide utile là où d'autres signes de la maladie manquent.

4. L'analyse génétique suggère clairement une ascendance dominante dans 4 familles. Ceci en est très probablement de même pour 3 autres. Dans les autres cas, l'étiologie ne pouvait pas être établie avec certitude. Les différentes interprétations génétiques sont discutées.

5. Bien que le nombre de cas soit restreint, il représente suffisamment de données pour justifier un calcul du taux de la morbidité pour les frères et sœurs des malades eux-mêmes. L'indice observé chez les enfants dont les deux parents sont touchés x non-touchés est compatible avec la supposition d'une simple ascendance dominante.

6. Il y a des preuves que la maladie peut déployer un degré différent de manifestation dans une certaine famille. On n'a pas pu démontrer cliniquement de différence si la maladie touche une famille ou des cas isolés.

7. La pathogénèse du rachitisme primaire résistant à la vitamine D est brièvement discutée.

Primäre (genuine) Vitamin D-resistente Rachitis. IV. Eine klinische und genetische Untersuchung.

1. Es wurde eine klinische und genetische Untersuchung primär Vitamin D-resistenter Rachitiker vorgenommen, die basiert ist auf 27 klinisch befallene Fälle, verteilt über 14 Familien. Davon waren 7 Einzelfälle; 8 Sekundärfälle — Eltern und Säuglinge der betr. Versuchspersonen — wurden als definitiv oder mutmasslich „subklinisch befallen" bezeichnet.

Die als „subklinisch befallen" Fälle bezeichneten wiesen eine leicht ansteigende alkalische Serum-Phosphatase-Aktivität, geringe Deformationen sowie röntgenologisch Skelettveränderungen auf. Diese Befunde deuten eine umfangreiche, wechselnde Ausdrucksäusserung des Zustandes an.

2. Der Ausbruch der Krankheit scheint nicht auf ein bestimmtes Lebensalter beschränkt zu sein, jedoch gewöhnlich wird das 2. Lebensjahr betroffen, so dass bestimmte klinische Zeichen der Erkrankung schon in sehr früher Kindheit nachweisbar sind. In 2 Fällen war das Befallensein schon in der praenatalen Phase signifikant nachweisbar.

3. Die alkalische Serumphosphatase-Aktivität erweist sich in Fällen, wo andere Zeichen der Erkrankung fehlen, als verlässlicher Führer.

4. Die genetische Analyse zeigt deutlich, dass bei 4 Familien eine einfache, dominante Vererbung vorliegt. Das Gleiche ist bei weiteren 3 Familien sehr wahrscheinlich. In den anderen Fällen konnte die Ätiologie nicht mit Sicherheit erwiesen werden. Verschiedene genetische Auslegungen wurden diskutiert.

5. Wiewohl das Material klein ist, ist es doch zur Beurteilung und Schätzung der Morbiditätsrate der Säuglinge unter den Versuchspersonen ausreichend gross. Die

beobachtete Rate für Kinder mit dem elterlichen Faktor „befallen:nicht befallen" stimmt mit der Annahme einer einfachen, dominanten Vererbung überein.

6. Es wurde deutlich, dass die Erkrankung einen unterschiedlichen Manifestationsgrad in einer einzelnen Familie aufweisen kann. Es zeigte sich kein klinisch demonstrierbarer Unterschied in dem Zustand, weder familiär noch als isolierte Erscheinung.

7. Die Pathogenese primär Vitamin D-resistenter Rachitiker wird kurz diskutiert.

Raquitismo primario (genuino) resistente a la vitamina D. IV. Estudio clínico y genético.

1. Se ha llevado a cabo un estudio clínico y genético del raquitismo primario resistente a la vitamina D, sobre 27 casos clínicos distribuidos entre 14 familias, de ellos siete casos eran aislados. Se clasificaron como subclínicos, ciertos o probables, ocho casos secundarios (padres y hermanos de los probandos).

Estos casos clasificados de subclínicos mostraban un ligero aumento de la actividad de las fosfatasas alcalinas del suero, pequeñas deformidades y alteraciones óseas radiológicas. Estas manifestaciones inducen a pensar en una amplia expresividad del proceso.

2. La enfermedad comienza a distintas edades, aunque habitualmente en el segundo año de la vida; sin embargo se demostraron signos clínicos ciertos en edades muy tempranas. En dos casos existian importantes datos en favor de su comienzo prenatal.

3. La actividad de las fosfatasas alcalinas séricas tiene gran valor en ausencia de otros signos clínicos.

4. El análisis genético sugiere claramente la existencia de un caracter hereditario dominante en 4 familias. Otras 3 familias respondían probablemente al mismo caracter. En los restantes casos no pudo establecerse con certeza su etiología. Se discuten varias interpretaciones genéticas.

5. Aunque la casuística es pequeña, es suficientemente representativa para justificar el cálculo de la morbilidad en los hermanos de los probandos. El índice observado de niños con hermanos afectos por los no afectos guarda relación con la hipótesis de un caracter hereditario dominante simple.

6. Se demostró que la enfermedad puede cursar con manifestaciones diversas en una misma familia. El proceso no presentaba diferencias demostrables clinicamente cuando se presentaba en una familia o de modo aislado.

7. Se discute brevemente la patogenia del raquitismo primario resistente a la vitamina D.

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Section of Pediatrics and School Hygiene of the Swedish Medical Society

Meeting, March 14, 1958

S. Kraepelien and K. Linneroth: **Hypersensitivity to acetylsalicylate in children.**

In view of the large use of acetylsalicylate compounds in pediatric practice, the risks involved in using these preparations are stressed, and in connection with this a case is reviewed of a marked allergic shock reaction in an 8-year-old asthmatic girl after ingestion of 0.5 g acetylsalicylate.

E. Hofman-Bang and O. Naglo: **Diabetes mellitus in a 17-day-old infant.**

Diabetes mellitus in infants is rather unusual. Cases in which the disease appeared prior to the age of one month total approximately ten in the world literature. At the Sachsska Pediatric Hospital in Stockholm a 17-day-old boy was admitted in diabetic coma. No diabetes in the family history. Pregnancy and delivery normal. Birth weight 3720 g. On admission deeply unconscious. No signs of infection. Markedly dehydrated. Deep breathing. Blood sugar 844 mg%. Glycosuria, ketonuria, proteinuria. Treated with regular insulin 4–8 units every 3–4 hours during the first day together with sodium bicarbonate, Darrow's solution and an amino acid–glucose preparation intravenously. The patient recovered quickly, awakened completely from his coma. Convulsion-like twitchings in the right half of the face. CSF straw-yellow, increased protein, 10 RBC and WBC per mm^3. EEG: epileptogenic activity from a left-sided focus. Despite decreased insulin doses hypoglycemic shock on the third day. Immediate good effect with intravenous glucose. Put on three units protamine insulin daily. Extremely difficult to maintain balance between insulin reactions and diabetic coma. After several months celiac symptoms. Very slow weight increase. Delayed motor development. Picture of nephrosis from age 3½ years. Died in lung edema at 3 years 7 months. Section: remains of old intracerebral hemorrhage in left corpus striatum. In the pancreas signs of chronic inflammation. The Langerhans islands small and scarce. Fresh inflammation in one adrenal. In the kidneys tubular changes as in nephrosis, glomerular changes less pronounced. The etiology of the patient's diabetes is discussed. Most probable cause is the changes in the pancreas. Possibly the old brain injury could have caused diabetes. Long-term prognosis very uncertain.

A. Alvin: **Is a Poison Center needed?**

With regard to this question, material covering 5 years (1953–1957) from the Sachsska Pediatric Hospital in Stockholm was gone through with regard to poisonings and suspected poisonings (1026 cases; all had stomach lavage, 41 cases were admitted,

2 dead). The age distribution of the material is in agreement with that of earlier investigations (95% of the cases concerned children younger than 5 years of age). A correlation of the number of cases of poisoning per year and the corresponding number of children in Stockholm under 5 years of age during the same time period immediately revealed an increase of frequency despite the intensified propaganda. The variations in the causative group (tobacco, poisonous plants, chemical-technical preparations, "aniline pencils") was insignificant during the period. The size of the causative group in percent of the total number of cases was: tobacco 43.8%, pahrmaceutical preparations 24.0%, poisonous plants 3.7%, chemical-technical preparations 23.4%, and "aniline pencils" 5.1%. The difficulties in determining whether to wash the stomach or not and a possible specific treatment in true or suspected poisoning is discussed from the basis of the division into the above causative groups. One then finds the greatest problems in the group comprising chemical-technical preparations, problems which include difficulties in finding out about the preparation's chemical composition, the poisonous character of the components and whether poisoning with these demands a specific treatment or not. It becomes apparent that when it is a case of a physician on duty attempting to answer these questions, he must depend on telephone questioning of hardware and chemical firms, or at best on contact with the producers in the case of Swedish products. The information thus gained is often, unfortunately, indefinite, and that has as a consequence that many stomach pumpings are done "for safety's sake", which is not satisfactory. The imported products can occasionally be found in the foreign books of toxicology. With regard to the group of pharmaceutical products it is pointed out that apparently common drugs and those which are regarded by many as not dangerous can cause very serious poisoning (salicylic acid, different iron tablets), and that the general public in direct questioning of doctors have received, unfortunately, misleading answers. When it is a question of the much-discussed "aniline pencils", it has been found that stomachs are lavaged in many cases unnecessarily. The coloring material in the Swedish and Danish pencils is the non-dangerous methyl-violet and not aniline. The same is true probably for those pencils made in Western Germany and England. In cases of poisoning with plants or fruits the initial difficulty is often to obtain identification of the plant from the description of the person who has been caring for the child. In this case a great need would be filled by a richly-illustrated "toxicological flora". In order to produce the possibility of quick and correct treatment of poisoning and in order to correctly answer questions concerning suspected poisoning, it is recommended that a Central Registry (Poison Center) be initiated which would be open around the clock to answer questions coming from doctors.

Discussion.—*M. Barr:* In order to get a general conception of what the small child at home meets in the form of chemical-technical preparations, an inventory was made of ten doctors' and pharmacists' homes as well as several grandparents' homes. All the preparations were so placed in at least one home so that they could have been reached by a clever 1½–2-year-old child. A review in tabular form comprises about 120 different preparations among which many strongly corrosive materials are met with such as caustic ammonia, pure hydrochloric acid, soldering material and cleaning material for drain and sewer pipes. In addition, several fluid organic hydrocarbon compounds were met with and insect material from DDT over parathione to 10% nicotine solutions. There are furthermore conserving materials of different types such as cuprinol. — *Pharmacist P. Å. Wikander:* Reports of the contents of various chemical-technical preparations should be able to be given by pharmacists who through their

knowledge of chemistry and their general view of poisons and non-poisons have had good experience in such matters. In the year 1956 reports from some 100 producers of chemical-technical preparations were collected by docent Berfvenstam with the support of the Swedish Medical Association. After these reports have been added to and eventually published, and after one has made sure that reports of new preparations are continually added to a card index, this should be placed in one or several duty pharmacies where pharmacists at any time of day or night should be able to give physicians information and advice. Pharmacist Rune Fagerström has reviewed the literature concerning cultivated plants to chart those plants and plant parts which have toxic contents and which can cause poisoning or symptoms of poisoning in children. The Folkhälsan has done a similar investigation which includes also mushrooms and plant sprays. — *B. Karlsson:* In a large number of cases it is not a question of poisonings but simply suspected poisonings or a narrow escape from poisoning. Only a very small number of those patients whose stomachs are washed out show signs of poisoning. If the series presented here is compared with the poisoning material published in 1955 from Crown Princess Lovisa's Pediatric Hospital (about 3200 cases) the results are about the same as regards the causes of poisoning. Propaganda against poisoning can result in people appearing more often for suspected poisonings. A positive result can, however, be present in that more serious poisoning conditions have occurred less often. To centralize the treatment of all narrow escapes from poisoning does not seem to be necessary. A Central Registry where the desired information could be given around-the-clock concerning possible toxic substances in different preparations would be of the greatest value. From that standpoint a Poison Center is needed. — *R. Berfvenstam:* The Swedish Medical Association has, together with Kalifa (an organization composed of most of the larger producers of chemical-technical products), discussed the possibility of setting up the service which is needed for quickly supplying information concerning poisonous ingredients in those chemical-technical preparations which appear in the Swedish home. About one hundred firms have freely given the information desired. The material has been classified into groups: certain additions are needed and in addition a scrutiny of the material for information concerning toxic doses, etc. In co-operation with Pharmacist Wikander in the Hospital Pharmacy, Karolinska Sjukhuset, these additions and the above-named scrutiny of the material will be made, after which a complete index could be set up.

E. Hagberg and C. Malmnäs: **Some cases of diaphragmatic insufficiency in newborns.**

After a short survey a review is given of 3 cases. *Case 1:* Isolated phrenic paralysis caused by birth injury of the brachial plexus. *Case 2:* Left-sided, postero-lateral diaphragmatic hernia with death 25 minutes after birth. On the basis of asphyxia the child was treated with, among other things, oxygen in the stomach which caused displacement of organs to the right. *Case 3:* Left-sided, postero-lateral diaphragmatic hernia which could be operated. Attacks of cyanosis 5 hours after birth. The heart murmurs in the normal position, but impure breath sounds were heard from the most inferior portion of the left hemi-thorax. A few hours later the heart sounds were heard furthest out in the right lower side of the chest, and the diagnosis was verified by X-ray. Operation carried out as a life-saving procedure. Stomach, small intestine, the larger part of the colon and the spleen were replaced in the abdominal cavity and the defect was closed. One and a half days after operation the patient died because of lung hypoplasia.

DISCUSSION.—*O. Öberg:* Various authors have emphasized that diaphragmatic hernia is a serious malformation. In 1925 Hedblom reviewed the literature and found that with "conservative" treatment 75% of the patients died within a month. Today everyone regards the correct method of treatment as operating as soon as possible regardless of how small the child is and regardless of how much the hernia is affecting respiration. The mortality has now been reduced to about 15%. Those hernias which require the quickest surgical intervention are the ones without a hernial sac which allow a free prolapse of viscera to the pleural cavity and cause a high degree of lung collapse on the affected side. Many of these patients also die before the diagnosis is made. One ought to have diaphragmatic hernia in mind when one sees a newborn child with dyspnea, cyanosis and vomiting. At Crown Princess Lovisa's Pediatric Clinic during the period 1947–1957, 17 patients with diaphragmatic hernia have been operated on. 25% have been hiatus hernia, 75% postero-lateral. The operative mortality has been about 11%. — *E. Hagberg:* We have had a case which died in the maternity ward and at post-mortem examination the stomach, the larger part of the small intestine, the transverse colon and the spleen were found in the thoracic cavity. The diaphragm had a defect the size of a little finger-nail, showing that the prolapse into the thoracic cavity had occurred at an early stage of fetal development.

I. Alm: **The difference in perinatal mortality between two maternity hospitals in Stockholm.**

Perinatal mortality in the city of Stockholm (800,000 inhabitants) for the year 1957 was preliminarily 1.85%: 206 children died during the year and 11,117 were born living. This mortality figure is somewhat higher than 1956 when it was 1.67%. With such a low mortality, differences in collection of the material in different maternity hospitals can more easily be of importance. A comparison of the two largest maternity hospitals was conducted to see to what degree the registration of newborns actually followed the strict regulations that all those with a birth length of 35 centimeters are included, and regarding those children that breathed, also those under 35 cm length. The maternity charts from the years 1955–1957 were studied in the two maternity centers designated as No. I and No. II. The pediatric care is guaranteed to be according to the same standards since the author is responsible for this care in both places. No. I has a course for teaching midwives, and No. II is a former university clinic which still from time to time is used for teaching medical students. The difference in the area from which admissions come is that No. I takes mothers from the southern part of the city where construction of modern, standardized living quarters is taking place rapidly. No. II takes 35% of its admissions from the city and mostly from older sections of a rather well-situated character, as well as 65% partly from residential suburbs and partly suburbs with industries. A review of the registrations gave the result that in isolated instances wrong registration had occurred, but that these were of small consequence. These incorrect registrations were divided equally throughout the 3 years and between the two institutions and they probably lack significance for the city's vital statistics. Almost all children in Stockholm are born now in hospitals. Other important data are reviewed in tabular form:

Maternity center:	I	II
Number births	10.086	8515
Stillbirths in %	1.67	0.97
Dead 1st week in %	1.29	0.93
Perinatal mortality in %	2.96	1.90

If the mortality in maternity center No. I could be reduced through social- and medical-prophylactic measures to the level of No. II, 100 children could have lived further during these 3 years. A review of certain social factors showed that the difference was large in certain respects. The examination showed that it was for the most part the young, unmarried mothers and their premature children which increased No. I's mortality, and also that the well-situated Stockholm people had a low stillbirth rate and comparatively larger children with low premature mortality. A review of the post-mortem material on almost all cases, as well as macerated fetuses, gave no definite difference in the institutions, although intracranial hemorrhage as a cause of death was a very infrequent finding in hospital No. II where the incidence of Caesarian section in cases of suspected complications was high. Congenital defects accounted for, in the entire perinatal mortality, 29 cases in hospital No. I and 20 cases in hospital No. II.

M. d'Avignon, Stockholm

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BOOK REVIEWS

E. Berger: **Zur allergischen Pathogenese der Cöliakie.**

S. Karger A. G., Basel, 1957. 55 pp., 11 figures. Price Swiss fr. 9.60.

The important discovery by Dicke, van de Kamer and Weijers that infants with celiac disease do not tolerate gliadin has thrown new light on the etiology and pathogenesis of this disorder. The mechanism of this intolerance has, however, not been well understood. The author of the present monograph has studied the antibodies against cereal proteins using a complement fixation reaction. These antibodies occur in children with celiac disease, but also to a large extent in a control material, increasing with advancing age. One important difference between children with and without celiac disease is, however, that these antibodies disappear from the sera of the former following administration of the antigen, e.g. gliadin. The antibodies of the sera of the control children are essentially uninfluenced and not bound by the antigen in question. This fundamental difference, described by the author, constitutes a valuable contribution to the basic understanding of the celiac disease, although so far only a small number of cases have been studied. The specific antigenic behavior of different cereal proteins is furthermore closely correlated to the presence or absence of intolerance symptoms, following their ingestion in celiac patients. The author concludes from his results that the gliadin intolerance found in celiac disease is a true allergic phenomenon.

B. Hellström

Martin Wrete: **Die kongenitalen Missbildungen, ihre Ursachen und Prophylaxe.**

Almqvist & Wiksell, Stockholm, 1955. 321 pp., 284 figures. Price Sw. Kr. 40.—.

In spite of the fact that this book appeared nearly three years ago, there is still reason to mention it in these pages. How important and topical the subject is becomes evident from the program of the Congress of the German Association of Internal Medicine in Wiesbaden this year, where the etiology of malformations is one of the main topics. For the pediatrician I think the prenatal period in human life has become the most important one in those countries where malnutrition, deficiency diseases and tuberculosis are no longer great problems in the postnatal period. Wrete is Professor of Anatomy in Uppsala and has made important research in embryology, which explains his interest and knowledge also in the field of teratology. His book consists of two parts, the first one dealing with the morphological development of the fetus, the influence of malformations upon the viability, frequency, etiological problems and possible preventive measures. The title of the book is perhaps a little misleading, as the second part, consisting of five sixths of the whole book, is descriptive, conventionally disposed

according to the different organs or tissues. This part constitutes an extremely good manual for students and doctors, and the description is illustrated by a very good choice of figures, some of them with criticism gathered from the medical-historical and the ethnological literature. The first part is from many points of view the most interesting. Since Greggs (not mentioned among the numerous references) in Australia published his cases of rubella embryopathy, the importance of viruses as etiological agents in malformation has been clear. After Greggs we have seen an enormous interest arise in the whole field of the etiology of malformations. Wrete gives an account of all the different agents which are known to be or which are presumed to be causes of fetal damage. During the last decade there has been a great deal of experimental work done, the most important by Ingalls and Warkany. Wrete pays attention to the results of the investigators mentioned, i.e. the significance of the biogenetic time factor. This means that the organs and the tissues are specially susceptible to damage in the very moment of maturation or synthesis. Another chapter, which in an eventual new edition of this book will be still more comprehensive than in this edition, deals with fetal damage by radiation. This growing problem has genetic aspects as well as aspects of the direct risk for the fetus. The difficulty in distinguishing the genetic factors and the exogenic factors in the etiology of malformations is stressed by the author. In prophylaxis one has to pay attention to both and not forget the psychic factors among the exogenic ones. Wrete's book makes a very topical and needed survey of teratology and is warmly recommended, not least to the pediatricians and the obstetricians.

Lars Ström

P. Gegesi Kiss and L. Barta: **Diabetes Mellitus im Kindesalter.**

Verlag der Ungarischen Akademie der Wissenschaften, Budapest, 1957. 384 pages, 53 figures. Price U.S $ 8.00.

The authors refer in the foreword to Claude Bernard who once stated that in diabetes there was no more to be learned by the clinicians. All the rest of the answers should come from the physiologists and the chemists. Being clinicians themselves, the authors deal with the clinical features of diabetes in more than two thirds of their book. In the first chapters, however, they make an excellent review of our actual knowledge of the physiology and chemistry in diabetes. Perhaps one could discuss the use of all the tolerance tests they are recommending as necessary in routine. Especially in childhood I think the starving test, for example, might be too risky.

About the frequency of diabetes the authors designate 2–3 % of all the inhabitants in different countries as diabetic, and of all diabetics 5.8 % are children according to Nelson. In this disease I think we are justified in speaking about the geography of diseases. The difference in frequency is remarkable if we think of the countries of the north-western area of the world from the Scandinavian countries to the Pacific, where the frequency is rather high, 10–20 %, and the Mediterranean countries, where the frequency is much less.

In the clinical part the chapter of coma and its treatment is a concentrate of Kiss' book of Coma diabeticum, recently referred to on these pages.

A question often discussed in the literature is whether an increased growth of the child means a prediabetic stage. The experience of the authors that an increased growth

is of no value deviates from the opinion of other authors, and they even stress that underweight is characteristic for the prediabetic stage.

Regarding the clinic of diabetes, the authors also give a good survey of the more uncommon features and the correlations to other diseases. They pay the proper attention to the important problems of late complications from the vascular system.

Also, concerning the late complications, I think there is an important difference in the frequency in different countries, and this may be explained by the fact that the authors are not quoting the papers of Lundbæk, being the scientist who works in a country where the late complications of diabetes are a reality of another magnitude than in the authors' country. Whether these complications have a close correlation to the special features of juvenile diabetes or not we don't know. Neither do we know if those special features are the susceptibility to insulin or the disposition to ketosis.

A good survey is given of the insulins. The experience that it is always difficult to regulate childrens' diabetes with zinc-protamin-insulins, I think, nowadays, is quite general. A short review is given of the oral preparations.

As for the diet, the authors recommend a diet relatively rich in protein and carbohydrates and poor in fat. It should be restricted but not within too narrow limits. I think we are inclined now to state that the conception of "free diet" has outlived itself. Still, I am of the opinion that a little difference in the dietary treatment of diabetes in childhood and in adult life is indicated. I agree with the authors that one has to follow the following four principles in the treatment of diabetes: a true dosage of insulin, a corresponding diet, a corresponding manner of living and regular controls by the doctor.

Lars Ström

von Harnack, G.-A.: **Nervöse Verhaltensstörungen beim Schulkind, eine medizinisch-soziologische Untersuchung.**

Georg Thieme Verlag, Stuttgart 1958, 92 pp. Price DM 9.80.

Of 2391 children beginning school who were examined by the author in 1952, 1335 were re-examined in 1956. The children, who were then 10–11 years old, were regarded as composing a representative selection of the Hamburg populace. The examination's purpose was to determine objectively establishable behaviour disturbances and to correlate these with certain environmental conditions. The following symptoms were dominant in boys: nail-biting, motor hyperactivity, agitated sleep, teeth grinding during sleep, enuresis, ties, head- or body-rolling, night frights and stuttering. In the girls difficulty in falling asleep was dominant, thumb-sucking and somnambulism. The homes were divided into five social groups. Children with behaviour disturbances were significantly more common in the lower than in the higher social groups. Likewise, the pathological environmental conditions. Most of the children with behaviour disturbances were seen among children from divorces and children born out of wedlock. Children from such environments showed especially sleep disturbances, hyperactive motor-symptom pictures, enuresis and disturbances of appetite. Children with obviously nervous mothers developed disturbances more often than those who had a quiet and harmonious mother. Children of mothers who had half-day jobs did not develop any increased degree of disturbances, while those whose mothers

(in complete families) had full-day's jobs outside the home showed a significantly increased frequency of sleep disturbances. The author explains this through such mothers being to tired to satisfy the childrens' need for contact when they come home from work. The true big-city children from the central city districts did not have greater frequency of behaviour disturbances than children from the outer districts or suburbs. Contrary to this one could determine in the former in significantly greater frequency vegetatively conditioned symptoms in the form of recurrent headache or abdominal pain, dizziness or fainting spells. The author assigns this to the fact that they are more susceptible to chronic noise. The single children indeed showed an increased frequency of sleep disturbances, but the author believes this is apparent and dependent thereon that single childrens' parents notice such symptoms more easily. It was furthermore seen that single children showed only an insignificant increase of behaviour disturbances; the frequency of enuresis in them was lower than in children with siblings. Single childrens' school performances were also better, they were less often left behind and did not disturb classes as often. Symptoms of depravity could not be demonstrated in the single children from complete families. The author bases these relationships on the fact that such children receive more care, contact and help than other children. Nor in the case of late-born children (with at least 10-years interval from the preceding sibling) is the pathogenetic significance of this special growth situation especially pronounced. In conclusion it can be said concerning nervous behaviour disorders that these disturbances which have larger "ego-proximity" such as difficulty in falling asleep and refusal of food are dependent in larger degree upon inadequate environmental conditions than are localized motor phenomena such as stuttering, tics and the like. Depravations and similar symptoms of an activity type (stealing, brutal actions, vagabonding and such) are, according to the author, often genetically anchored but sometimes are expressions of a neurosis. The environment contributes, however, to a great degree to their origin: on the average they occur twelve times more often in children from incomplete families and disturbed families in comparison with those children from complete families. The vegetatively conditioned symptoms were not dependent in larger degree on the familial environment, something which can be an expression of the fact that they are for the most part constitutionally conditioned. Contrarily, as mentioned, the bigcity environment has an effect. The author has also examined the relation between school performances and home environment and found that the nervous mothers had the highest percent of children with bad school grades and poor concentration. Children born out of wedlock and those from divorces were to a greater degree than others those who were left behind or transferred to a help class. The examination speaks further for the fact that those children who are often defective in intelligence and who have had postponement of entry into school manage poorly. Of the younger children who are mature enough for school early, a portion get along almost as well as those of regular school age. If one, however, studies their school progress up to the age of ten years, it is seen that of those of normal age 15% had repeated a class, of the relatively young 20%, and of those who started too early 24%. The author therefore pleads that it be rigorously held to that children who are not mature enough for school receive postponement of starting school, and that those children who are clearly defective in intelligence be placed in help classes as early as possible. Of those children who disturbed classes about twice as many came from imcomplete families as from complete families. The author believes himself able to say that the schoolchildren up to the age of 10 years are not over-exerted in school. He bases this on the fact that the frequency of nervous behaviour disturbances

decreased from the time the children entered school to the time they reached ten years of age. The number of children who are seriously threatened or disturbed from a psychic viewpoint is estimated by the author to be 5–6%. The results presented here are the most important ones. The investigation is carefully carried out and the book contains many valuable viewpoints. It can therefore be warmly recommended.

T. Ramer, Stockholm

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CASE REPORT

Female Non-Adrenal Pseudohermaphroditism

by LARS R. NILSSON and LARS SÖDERHJELM

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The simplest classification of the condition of ambisexual differentiation is based on gonadal type. In the case of male pseudohermaphroditism the gonads are testes, in female pseudohermaphroditism ovaries, and in true hermaphroditism both structures are represented, often situated together in common glands, "ovotestes". Cases of gonadal dysgenesis may be considered as a fourth group (5).

Female pseudohermaphroditism is usually caused by congenital hyperplasia of the adrenal cortex with a marked increase in the secretion of androgenic substances (17). Arrhenoblastoma during pregnancy has been described as resulting in pseudohermaphroditism in a female foetus (17). Female pseudohermaphroditism has recently been reported in children whose mothers received testosterone treatment during the first months of pregnancy (6, 8). The occurrence of the condition in the absence of adrenal cortex hyperplasia or other demonstrable hormonal influence is rare. About 20 such cases have been published (2, 3, 9, 10, 13, 14, 17).

We have recently observed a case of this type, presented briefly as follows:

First-born child to unmarried mother. Birth weight 3040 g. Family history revealed nothing relevant. Mother was anaemic during pregnancy. Normal, full-term delivery. Genital malformation was noted with enlarged phallus, behind which a small orifice was present. The labia were fused and showed traces of scrotal creases bilaterally (Figs. 1, 2). The uro-genital opening was too small to permit instrumental examination, but X-ray following the injection of contrast substance revealed a "male" urethra-like outlet, which divided cranially into one duct to the urinary bladder, and another which branched off dorsally at right-angles to the first and then continued cranially. This second duct terminated in a space corresponding to the vagina (Fig. 3) in the upper pole of which a thinning of the contrast in the shape of a cervical outline could be seen (Fig. 4).

The findings indicated a case of virilism of the external genitalia. Urinary 17-ketosteroids, however, were found to be 0.43 mg/24 hours at the age of one week. A follow-

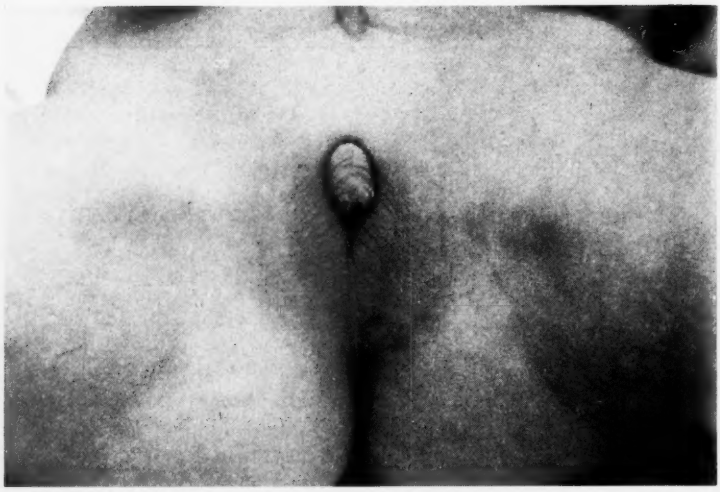

Fig. 1. External genitalia (at the age of two years): enlarged clitoris, fused labia with scrotal folds.

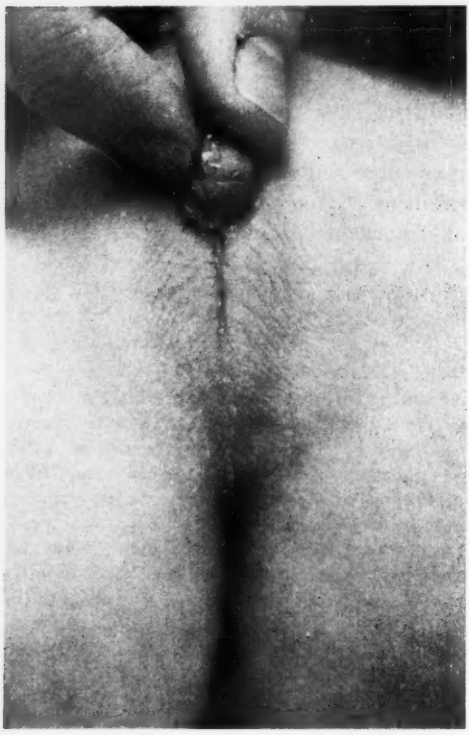

Fig. 2. Small urogenital opening at the base of phallus.

Fig. 3. Contrast injected into the urogenital opening visualizing a male type of urethra with communication with vagina.

up revealed no progression of virilism and at 3 months of age, the 17-keto-steroids were 0.54 mg/24 hours. The mother was advised to bring up the child as a girl.

The child was admitted, aged 22 months, for further investigation. Genital status was unchanged: 17-keto-steroids now 0.2 mg/24 hours. Sex determination using buccal epithelial scrapings was carried out by Dr. Povl Riis, Copenhagen, and revealed chromatin-positive nuclei, i.e. female sex.

Explorative laparotomy was carried out by Ivar Sandberg, Skellefteå, with the following findings: Uterus and tubes normally situated. Right ovary elongated and of normal size: left ovary similarly elongated but smaller. Biopsy taken from the glands on both sides showed immature ovaries with numerous primary follicles. Testicular tissue could not be demonstrated (C. Lundmark, Stockholm). The patient is to undergo plastic surgery in the near future.

Discussion

In congenital abnormalities of the sexual organs external examination gives little guidance as to the precise type of intersex present. In true hermaphroditism all possible combinations of male and female features are to be found. Male pseudohermaphroditism can be accompanied by a typical

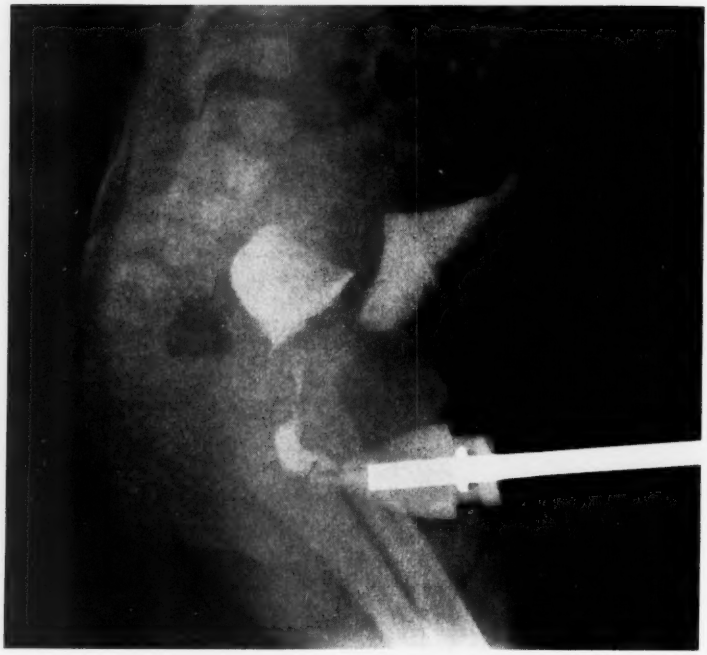

Fig. 4. Contrast injected through urogenital opening into the vagina, where the contours of portio uteri are seen. The bladder is filled with contrast through excretory urography. (Roentgenograms by Dr J. Baumgartner.)

female appearance, but all gradations are found between the latter and male cryptorchidism with hypospadia (17). Female pseudohermaphroditism secondary to adreno-cortical hyperplasia can present a mere hypertrophy of the clitoris or a clitoris resembling a true penis, and be accompanied by fusion of the labia to give the appearance of a scrotum (15).

The non-adrenal type of female pseudohermaphroditism is also accompanied by great variations in appearance (18), though hypertrophy of the clitoris is seldom of the severe degree, sometimes found in the adrenogenital syndrome (3). As a rule urethra and vagina share a common external orifice, but separate openings are present in a number of cases. In four cases a penile urethra was found, ending at the tip of a penis-like clitoris: furthermore in all these cases there was a communication between urethra and vagina (4, 9, 14).

Valuable information can be gained by internal palpation, urethrovaginoscopy and X-ray examination after injection of contrast. Male

pseudohermaphroditism can be accompanied by a fully developed vagina, which, however, in most cases ends blindly. The existence of a properly developed portio uteri and uterus is a strong indication that the condition is one of female pseudohermaphroditism. Howard & Hinman (9) claim that non-adrenal female pseudohermaphroditism is the only type of intersex in which one sees the urethra open into the vagina. Otherwise there are no reliable anatomical criteria to distinguish between the two varieties of female pseudohermaphroditism (18).

Our own case had a large phallus and a small urogenital orifice behind it. The labia were fused in the mid-line to suggest a scrotum, but no gonads could be palpated. X-ray with contrast injection revealed a vagina of normal size and distinct cervical outline, a large urinary bladder and a direct communication between urethra and vagina corresponding to the utriculus prostaticus (Figs. 3 and 4).

The anatomical findings led to a diagnosis of female pseudohermaphroditism. Initially we suspected adreno-cortical hyperplasia, since it is by far the most common cause of this condition. The 17-keto-steroid values, however, were normal and further observation revealed no sign of progressive virilism. The diagnosis of non-adrenal female pseudohermaphroditism was confirmed by laparotomy with biopsy from both gonads.

When the sex of a new-born infant is in doubt further management of the case after a careful external examination can be outlined as follows:—

(1) Instrumental examination of orifice(s) where technically possible.
(2) X-ray examination following injection of contrast.
(3) Genetic sex determination. The best method is chromatin examination of scrapings of buccal epithelium and vulval epithelium where available (16). The value of this test is limited only by the fact that hermaphrodites can possess chromatin of either masculine or feminine type (1).
(4) Measurement of 17-keto-steroid excretion.
(5) Explorative laparotomy and bilateral gonad biopsy.

Laparotomy can be performed in the new-born, but is usually undertaken when the child reaches 1–2 years. In confirmed cases of congenital adreno-cortical hyperplasia there is no necessity for laparotomy, the internal anatomy here being rather uniform (16). In other cases, however, operation is essential for the determination of gonadal type, and to discover precisely which organs are present. Biopsy from the gonads should be bilateral keeping in mind the possibilities of a true hermaphroditism.

An early diagnosis in cases of ambisexual development is of great importance. Female pseudohermaphroditism secondary to adreno-cortical hyper-

trophy should be diagnosed immediately after birth. Many such infants soon develop signs of failing adreno-cortical function, which must be recognised and treated at once. Progressive virilism must also be halted by the early administration of cortisone therapy. From the point of view of differential diagnosis two interesting cases of female pseudohermaphroditism were reported by Papadatos & Klein (13). These patients developed signs of electrolyte disturbance around the age of 3 weeks. This was not the result of commencing adrenal failure but of renal damage of the "salt losing nephritis" type, secondary to congenital obstruction of the urinary tract.

Early diagnosis is of course of the utmost importance to the parents and for the child's psychological development. It has been shown that the gonads themselves play little part in the subjective experience of sex. It is the parents' attitude and the reactions of other contacts which lead to the child's accepting itself as a boy or a girl (11, 12). This conviction develops early in life and is quite established by the age of 18–30 months. Change of sex at a later date can lead to serious psychological disturbance (7). In patients with male pseudohermaphroditism or true hermaphroditism, sex is decided principally from the appearance of the external genitalia, in other words the patient's possibilities of acting as a man or a woman (12, 17). The same principle was formerly taken as a guide to management in female pseudohermaphroditism of adrenal origin, but with early cortisone treatment it should be possible to bring up all such children as girls. In non-adrenal female pseudohermaphroditism the decision must not be influenced by the appearance of the genitalia, but again all such cases should be regarded as females (16). Their internal anatomy is female, they develop feminine traits at puberty, and after plastic surgery they can be assumed to have the same possibility as other women of becoming pregnant.

Female non-adrenal pseudohermaphroditism is the form of intersex with the most obscure aetiology. One has talked of adrenal hypersecretion during certain periods of foetal life, and of masculinizing hormones from the mother or the placenta (18). The case described by Perloff *et al.* (14) had a normal twin which casts doubt on the hypothesis of hormonal or other influences from the mother. Howard & Hinman (9) regard the abnormality as a localised developmental failure, with delayed union between the distal ends of the Müllerian ducts and the urogenital sinus, which in turn leads to the development of the phallus in a masculine manner. Adreno-genital cases do not display a tendency to malformations of the urinary tract (9), whereas the non-adrenal types are often accompanied by urinary tract abnormalities (9, 13), which supports the belief that genital malformations in the latter cases are not brought about by genetic or hormonal influences, but are instead simple developmental defects.

Summary

A case of non-adrenal female pseudohermaphroditism is described. An outline is given for the establishment of the diagnosis in new-born infants with conditions of ambisexual differentiation.

Pseudo-hermaphrodisme non surrénal chez un enfant du sexe féminin.

L'auteur décrit un cas de pseudo-hermaphrodisme non surrénal chez un nouveau-né et donne quelques indications pour l'établissement du diagnostic chez les nouveau-nés qui présentent des caractères des deux sexes.

Weiblicher, nicht nebennierenbedingter Pseudohermaphroditismus.

Ein Fall von nicht nebennierenbedingtem Pseudohermaphroditismus bei einem neugeborenen Kinde wird beschrieben. Ein Entwurf für die Diagnosenstellung bei Neugeborenen mit den Bedingungen für ambisexuelle Differenzierung wird angegeben.

Seudohermafroditismo femenino no adrenal.

Descripción de un caso de seudohermafroditismo no adrenal en un recién nacido. Directivas para determinar el diagnóstico en recién nacidos con las condiciones de diferenciación ambisexual.

Addendum:[1]

The patient's mother had hyperemesis gravidarum and received during parts of the third and fourth gestational months 25 mg daily of metandriol, a steroid with anabolic effect and weakly androgenic properties. The mother experienced no virilization. This steroid therapy, however, must be considered as the cause of the virilization of the infant.

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[1] This addendum illustrates the necessity of careful investigation regarding untoward artificial production of hormonal disorders by hormone treatment of the mother before determining the cause of an endocrine disturbance in newborns and infants.

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Aetiology of Non-Diphtheritic Croup

II. Virologic Investigation

by L. PHILIPSON

The bacteriologic aspects of non-diphtheritic croup have been considered previously (10, 16). A virus aetiology has been suggested for the subglottic type (16) and recently some evidence has been presented by Chanock of an association between non-diphtheritic croup and a new type of myxovirus (1). Philipson & Wesslén have reported the recovery of a cytopathogenic agent from cases of non-diphtheritic croup and from Day-Nursery children (12). The virus found was called U-virus and has been associated with upper respiratory disease (14, 15). It was further found that this agent was serologically distinct from that isolated by Chanock (12).

The present paper reports the virologic findings and the serologic response to U-virus in children suffering from croup and in other groups of children.

Clinical Material

Non-diphtheritic croup cases (Croup children)

During the period October 1956 to December 1957 patients admitted to the Ear, Nose and Throat Department of the University Hospital were examined for virus and bacteria from the throat and for virus from the faeces. The patients were referred from the Out-Patient Department with the diagnosis of non-diphtheritic croup. A total of 110 admittances were hospitalized with this diagnosis and 87 of these were investigated during the interval studied. The diagnosis was based on characteristic symptoms and indirect laryngoscopy. The majority of the cases selected for this study had a subglottic type of this syndrome, which type was found to be most common in a previous study (10).

The cases investigated during the period October 1956 to May 1957 are called *Croup children Group I* in this study. These 53 cases were carefully examined for bacteria on admission and discharge from the Hospital.

The cases investigated during the period October to December 1957 are called *Croup children Group II* (34 cases) in this study. Except for the virologic investigation, the histories of these children were carefully recorded and analyzed.

In Group II, comprising 34 Croup children, records were compiled by questionnaires concerning allergy in patient and family, infectious diseases of the last fortnight in the family, interval between signs of upper respiratory disease and croup symptoms in the patient, number of siblings of the patient and simultaneous incidence of croup or other respiratory disease in the siblings. Further, the weather at onset of the disease in cases of relapse was noted. These data were obtained in 18 cases of relapse and in 16 of initial attack.

The usual treatment at the Hospital included antibiotics of the tetracycline type, humidified air, antihistamines, and cortisone. The doses of cortisone used were 15 mg prednisone for children above 2 years old and half that dose for the children below 2 years. Prednisone was administered for 1 to 2 days, after which the dose was successively decreased. During the period October to December 1957, prednisone was not given to all patients, since preliminary results suggested lower titres of neutralizing antibodies in the treated cases.

Day-Nursery children (Nursery children)

A group of children from the Day-Nurseries of Uppsala was also investigated in this study. Specimens were taken from 10 children selected at random from all six Day-Nurseries of the town at intervals of one month during the period October 1956 to May 1957, in order to cover the whole infectious area and period.

Virologic and bacteriologic specimens and one serum specimen were taken from each child investigated. A total of 67 children were examined during the period studied.

Children from the Surgical Department (Casualty children)

A third series was collected from children attending the Out-Patient Surgical Department of the University Hospital as non-infectious emergencies. Only cases without a history of respiratory disease for 3 weeks prior to the date of the sampling were accepted. A total of 20 patients were assigned to this group from October 1956 to May 1957. One serum specimen and bacteriologic and virologic specimens were obtained from these children.

Methods

Sampling

Bacteriologic specimens.—Nose and throat swabs were taken and analyzed separately. From the Croup children, one specimen was taken on admission before the start of antibiotic therapy and a second specimen on discharge from the Hospital. From the Nursery and Casualty children, only one specimen was taken.

Virologic specimens: Throat swabs.—Throat swabs from the hypopharyngeal region were taken once from all groups of children. The swabs were taken as soon as possible after arrival at the hospital in the Croup groups. The swabs were immediately placed in tubes with bovine amniotic fluid with antibiotics (1000 units of penicillin and 1000 mcg of streptomycin/ml). This fluid was inoculated in quantities of 0.1 ml into each of 4 human embryonic lung tissue cultures after on the average 6 hours' storage at 4 C.

Faeces.—One faecal specimen was taken from each child in the different groups. The specimens were shaken with glass beads in bovine amniotic fluid with antibiotics (about 10 per cent faeces) and then centrifuged at 8000 r.p.m. for 10 minutes. The

supernate was inoculated in amounts of 0.1 ml into each of 4 human embryonic lung tissue cultures. Uninoculated culture tubes were always included for comparison.

Serum specimens.—Blood was taken by scalpel-cut in the thumb and collected in a specially devised sampling tube by vacuum pressure. Samples of sera were collected in the acute phase of the disease (one day after admission) and during convalescence (10 to 14 days after admission) from the Croup children. During the period October to December 1957 the convalescent sera were obtained 5 to 10 days after admission. Only one serum specimen was received from each of the Nursery and Casualty children. Paired sera from Croup children admitted to the Hospital during 1954 and 1955 were also tested for neutralizing antibodies. Because of insufficient serum amounts, these sera were not tested in the H-I test. These sera had been stored at − 20°C and thawed 3–4 times.

Technique

Bacteriologic.—The following media were used for culture: (i) Blood agar; (ii) haematin agar; (iii) gentian violet blood agar; (iv) phenol-mannitol agar with 7.5 per cent NaCl; (v) tellurite-haematin agar; (vi) ascites broth. All media were prepared according to methods previously described (10). The criteria for diagnosis of the pathogenic and potentially pathogenic bacteria were the same as described before (10).

Virologic: Tissue cultures.—Human embryonic lung cultures in a plasma clot were used for isolation of virus. For neutralization tests, cultures of trypsinized monkey kidney were used. Bovine amniotic fluid was used as maintenance medium for the tissue cultures. The method used for preparation and maintenance of the tissue cultures has previously been described (12). After inoculation with the different specimens, the culture tubes were read for cytopathogenic effect every second day for 14 days. The fluid of the tubes showing degeneration was passed to uninoculated tubes with tissue cultures by inoculating 0.1 ml amounts of the infected fluid into each of 3 tubes.

Neutralization.—Twofold dilutions of heated serum (56°C for 30 minutes), and an equal volume of virus estimated as 100 TCD50 (50 per cent tissue culture dose) per 0.1 ml of the prototype strain of U-virus, were incubated for 2 hours at 37°C and the mixture then inoculated in 0.2 ml amounts into each of 2 culture tubes. Acute phase and convalescent sera were examined simultaneously. The initial serum concentrations tested were serial dilutions from 1:2 to 1:512 when sufficient serum was available. Owing to serum shortage, the initial dilution was 1:4 in a few specimens. Simultaneous titration of the virus involved was performed in every neutralization test. Final readings were made 3 days after complete degeneration had occurred in the virus control tubes containing the estimated 100 TCD50. A fourfold increase in titre between acute phase and convalescent sera was considered significant for antibody increase caused by the virus infection. Some sera, which showed no antibodies in this test, were also examined for neutralizing antibodies by a method devised by Gard (3) modified as previously described (14).

Haemagglutination-inhibition (H-I).—To 0.25 ml of serial twofold dilutions of sera were added equal volumes of U-virus suspensions containing 4 to 6 agglutinating units. The serum-antigen mixtures were incubated for 1 hour at 37°C, after which 0.5 ml of 0.125 per cent human O-erythrocyte suspension in saline was added. The tests were read after 3 to 5 hours' sedimentation at 4°C. The highest initial dilution of serum giving complete inhibition of agglutination was considered the H-I titre of the serum. A more detailed description of the technique has been given elsewhere (13).

Typing of strains.—Nineteen strains of the agent isolated from the Croup and Nursery children were cross-typed as described in a previous paper (12). Further positive isolates were typed against a hyperimmune serum against the U-virus prepared in monkey and diluted 1:10. The titre obtained for this serum against the homologous strain was 1:512. Positive isolations which were not neutralized by this serum were further typed against hyperimmune serum against adenoviruses.

Clinical Considerations

Croup children

Most of the 75 children investigated in this study were between 1 and 5 years old, the age distribution being similar to that reported previously for this disease (10). Patients were hospitalized more commonly during the autumn and spring and the seasonal variation agreed with that described earlier (10). The frequencies of complications and of recurrences were also similar to those recorded before (10).

The case histories compiled by questionnaire from the Croup children Group II (34 cases) were analyzed. These comprised 18 cases of relapse and 16 of initial attack. The sex distribution was 22 boys and 12 girls. Three of the relapsing cases were reported by the parents to have allergic manifestations after exposure to food or pollen; among the initial attack cases 1 child was reported to have eczema. The families of the 34 children reported allergic manifestations in 6 instances, of which 4 were described as eczema.

Further, the records yielded some evidence that upper respiratory infections had occurred in 20 of the 34 families shortly before the onset of croup symptoms in the patients. In all but one of the relapsing cases, characteristic croup symptoms were reported as the initial symptoms of the disease observed. In 12 of 16 cases of initial attack, symptoms of upper respiratory disease preceded the croup symptoms by 1 or more days.

The parents of 10 of the 18 relapsing cases claimed that the croup usually developed during foggy or damp weather. In 4 of the 34 cases, croup symptoms had occurred simultaneously in a sibling to the patient. These instances occurred among the siblings of the relapsing cases. The 34 patients each had 1.5 siblings on the average.

Nursery children

The children investigated at the Day-Nurseries were chosen at random and selected only to match the Croup Group I as to age. The age distribution of the Nursery children is shown in Fig. 1. Twenty of the 67 children investigated suffered or had recently suffered from respiratory disease. The affections were mostly non-febrile with cough and/or coryza, but in

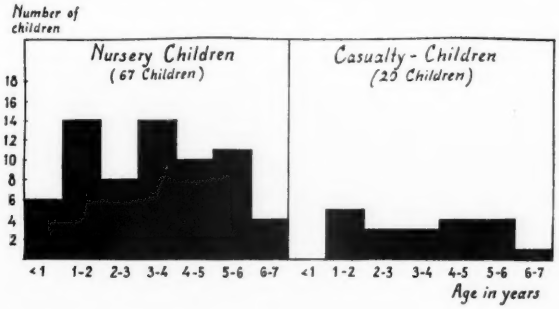

Fig. 1. Age distribution of the Nursery and Casualty children.

some cases fever accompanied the disease. Consequently, it would appear that there may be important bacteriologic and virologic deviations from the flora which might be taken as normal for the environment in which the Croup children lived. As has been reported before, respiratory infections may be extremely common in the Day-Nursery, depending on the lack of effective precautions taken to avoid them (5).

Casualty children

Among these children, the absence of respiratory disease for 3 weeks prior to the sampling was a condition of selection. All children investigated fulfilled these requirements. The age-distribution of these children is shown in Fig. 1.

Results

Bacteriologic findings

The bacteriologic findings in the Croup children Group I on admission to the Hospital and the Nursery and Casualty children are given in Table 1 for the bacterial species haemolytic streptococci, pneumococci, *Staphylococcus aureus* and *Haemophilus influenzae*. As is seen in Table 1, *Staph. aur.* was found in about 40 per cent of all three series. *H. infl.* was isolated in 7.5 to 10 per cent of the three groups. Pneumococci, however, were found in about 30 per cent of the Nursery children as against 5.6 and 10 per cent in the other two groups. Haemolytic streptococci were also more common among the Nursery children. Table 1 shows conclusively that pneumococci and haemolytic streptococci were isolated in higher frequency from the Nursery children than from the other two groups of children studied.

The bacteriologic specimens taken from the Croup children Group I on

TABLE 1

Bacterial isolation frequencies in per cent of bacteria considered pathogenic in Croup children Group I, Nursery, and Casualty children.

(The bacterial findings in the Croup children are those found in the sample on admission to the Hospital.)

Series	*Staph. aur.*	*Haem. infl.*	Haemolytic streptococci	Pneumococci
Croup children Group I (53 cases)	41.5	7.5	3.8	5.6
Nursery children (67 cases)	43.3	7.5	10.4	29.9
Casualty children (20 cases)	40.0	10.0	0.0	10.0

discharge from the Hospital showed the frequency of *Staph. aur.* to be slightly higher than on admission.

The frequencies of haemolytic streptococci, pneumococci, and *H. infl.* were as low or lower than those found in the tests taken on admission. Similar results have been reported previously (10).

Virologic findings

During the period October 1956 to December 1957, 75 non-diphtheritic croup patients admitted on 87 occasions were investigated for virus in

TABLE

Isolation of U-viruses in the Croup Gro

Period of time	Croup children				Nurs
	Total number of cases	Specimen from which agents were isolated		Positive cases	Total number childr
		Throat	Faeces		
Oct.–Nov. 1956	19[a]	8	5	11	1
Dec. 1956–Jan. 1957	15	2	1	3	1
Feb.–March 1957	14	1	1	2	
March–May 1957	5	1	0	1	2
Oct. 1956–May 1957	53	12	7	17	6
Percentage positive	—	22.6	13.2	32.1	—
Oct.–Dec. 1957	34	6	5	9	
Oct. 1956–Dec. 1957	87	18	12	26	
Percentage positive	—	20.7	13.8	*29.9*	

[a] Adenovirus type 5 was isolated from 3 of these patiens. These isolations are not included

throat and faeces by the tissue-culture technique. The results of this investigation and the results of virus-isolation attempts in the Nursery and Casualty children are shown in Table 2. As will be seen in Table 2, two different types of virus were found in the Croup children: one was adenovirus type 5, isolated in 3 cases during October 1956, the other was a virus slightly cytopathogenic for tissue cultures of human embryonic lung in the first passages apparently unrelated to viruses described previously (12). This virus has been called Uppsala-virus (U-virus) to facilitate the description of the agent. It was found in throat and/or faeces on admission to the Hospital in a total of 29.9 per cent of the croup cases. The corresponding frequencies for the Nursery and Casualty children were 11.9 and 0 per cent respectively. Eight of the 10 strains isolated from the Nursery children were recovered from the 20 children who suffered or had recently suffered from respiratory disease. Table 2 shows, however, that U-viruses were isolated in higher frequencies in the autumn than at other seasons of the year, although sporadic positive isolations were noted during the whole year. The isolation frequency in throat samples of Croup children appeared to be higher than that in faecal samples. In the Nursery children, the isolation frequencies were of the same order in both throat and faecal specimens.

Serologic investigation: Croup children

Paired sera from the Croup children were obtained in 63 cases. They were examined for antibodies by haemagglutination-inhibition and neutral-

TABLE

roup Gro... the Nursery and Casualty children.

Nurs...ildren				Casualty children			
Total number children	Specimens from which agents were isolated: Throat	Faeces	Positive children	Total number of children	Specimen from which agents were isolated: Throat	Faeces	Positive children
17	4	4	6	3	0	0	0
18	0	0	0	5	0	0	0
8	0	1	1	4	0	0	0
24	0	1	1	8	0	0	0
67	4	6	8	20	0	0	0
—	6.0	8.9	*11.9*	—	0	0	0

...included... table.

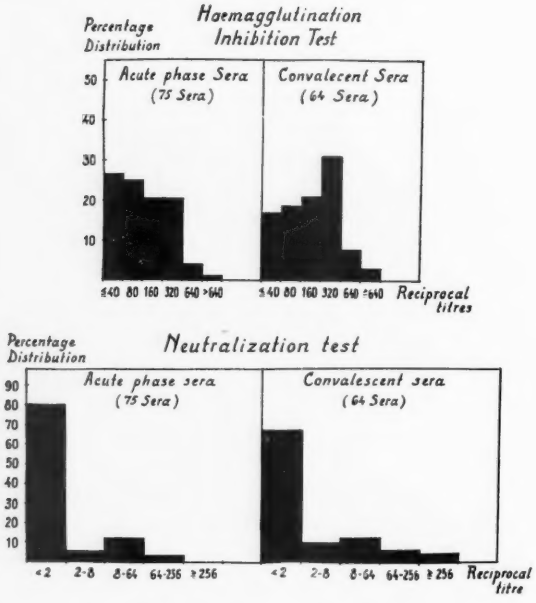

Fig. 2. Serological response to U-virus in the Croup children expressed as percentage distribution of neutralizing and haemagglutination-inhibiting antibody-titres.

ization tests. The results of these tests for all sera obtained are shown in Fig. 2. It has previously been shown that supposedly non-specific inhibitors in reciprocal titres of 20 to 40 against the haemagglutinin of the U-virus were present in human sera (13); consequently, only reciprocal titres of over 40 in the H-I test have any relevance as to specificity. As will be seen in Fig. 2, most Croup children showed antibodies in the H-I test in both acute phase sera and convalescent sera. A significant fourfold increase in H-I antibodies between the first and the second serum specimens was obtained in 15 cases (23.8 per cent).

A significant increase in neutralizing antibodies between the acute phase serum and the convalescent serum was noted in 14 cases (22.2 per cent). As will be seen in Fig. 2, 67 per cent of the croup cases showed no neutralizing antibodies in either acute phase or convalescent sera. Thirty-eight per cent of the cases showed a fourfold increase in titres between these two sera in either the H-I and/or neutralization test. Thirty-one paired sera in which methods in common use failed to demonstrate neutralizing antibodies were investigated by a more sensitive method, as described under "Method".

This method, which has been considered more sensitive in studies on other viruses (3) failed to detect neutralizing antibodies against U-virus in the sera negative to the neutralization test commonly used.

Influence of prednisone on the serologic response in Croup children

As it was thought that the cortisone treatment of the croup children might have led to an impaired antibody response in these patients, 114 paired sera from croup cases investigated before the introduction of prednisone treatment at the Hospital were tested for neutralizing antibodies according to general methods. These sera had been collected for an earlier investigation concerning the role of bacteria in the croup syndrome (10). They had been stored for 2 to 3 years at $-20°C$ prior to testing. Of the 114 paired sera, 17 acute phase and 25 convalescent sera showed neutralizing antibodies to the U-virus in higher reciprocal titres than 5. Thus, 15 per cent of these cases had neutralizing antibodies in acute-phase sera as against 22 per cent in convalescent sera. In 17.5 per cent of the 114 paired sera significant increases in neutralizing antibodies were obtained.

From October to December 1957, the indications for prednisone treatment were restricted. During the whole period, 43 children from whom paired sera were obtained were treated with prednisone and 20 children not treated. The paired sera from these children showed that neutralizing antibodies in reciprocal titres higher than 2 were present in the convalescent sera in 8/43 (18.6 per cent) children of those treated and in 12/20 (60.0 per cent) of those not treated with prednisone. The acute-phase sera showed neutralizing antibodies in 5/43 (11.6 per cent) of the treated and in 4/20 (20.0 per cent) of the non-treated patients. Forty-five per cent of non-prednisone-treated and 11.6 per cent of the treated cases showed significant increases in neutralizing antibodies. The convalescent sera were obtained 5 to 10 days after admission in most of the non-treated cases compared to 10 to 14 days in most of the treated cases.

Nursery children and Casualty children

The results of the H-I and neutralization tests of the Nursery children sera are given in Fig. 3. As is seen in Fig. 3, only 20 per cent of the children showed reciprocal titres above 40. Neutralizing antibodies were present in 30.0 per cent of the Nursery children, as is also shown in Fig. 3. The reciprocal titres varied from 4 to 512.

The correlation between H-I antibodies and neutralizing antibodies is presented in Fig. 4 for the Nursery children. The titres obtained in the sera of virus carriers are encircled. As will be seen in Fig. 4, some correlation between the two types of antibodies seems to exist, but in individual cases neutralizing antibodies were recorded in the absence of haemagglutination-inhibiting antibodies. Only in one case was a reciprocal titre of 80 observed

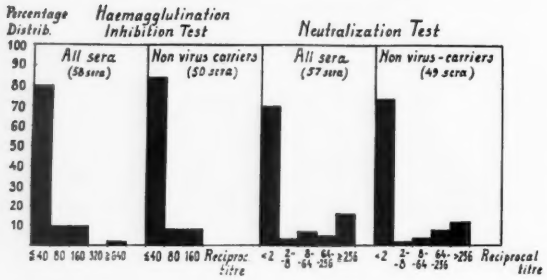

Fig. 3. Serologic response to U-virus in the Nursery children, expressed as percentage distribution of neutralizing and haemagglutination-inhibiting antibody-titres.

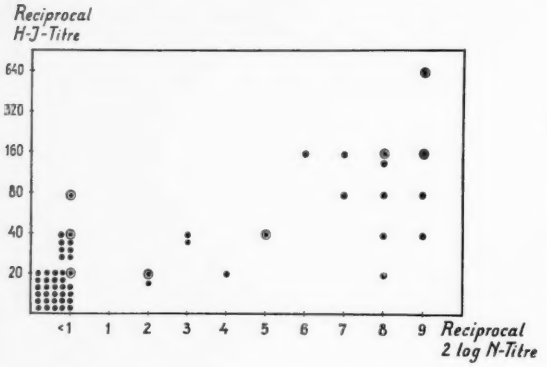

Fig. 4. Correlation between titres of neutralizing antibodies and haemagglutination-inhibiting antibodies against U-virus in the sera from the Nursery children. Sera of virus carriers are encircled.

in the H-I test in the absence of neutralizing antibodies. The Casualty children investigated showed H-I antibodies in reciprocal titres of 5 to 40 and no neutralizing antibodies with the techniques used.

Discussion

In the search for a causative viral agent of non-diphtheritic croup, a virus called U-virus was isolated. To the best of our knowledge this differs from those described previously (12). This agent was isolated in 29.9 per cent of the croup cases investigated on admission to the Hospital during October 1956 to December 1957 from throat and/or faecal specimens. It was also found in 11.9 per cent of Day-Nursery children, in whom an association between the findings and respiratory disease was difficult to prove as only single serum specimens were obtained from this group. Eight out of ten strains isolated in this group were, however, recovered from children, who suffered or had recently suffered from mild respiratory disease. Positive findings of neutralizing antibodies in 30 per cent and H-I antibodies in 20 per cent of the Nursery children indicated the U-virus to be

common in the Day-Nursery children during the studied period. In a separate study of a small epidemic of mild respiratory disease in a Day-Nursery some evidence was adduced for an association between U-virus and this disease (14). Further mild respiratory disease developed in some adults at transmission experiments with U-virus (15).

A third group of 20 Casualty children with no recent history of respiratory disease served as a control group and they had neither virus nor specific antibodies in their specimens.

The serological response against U-virus in the Nursery children (Fig. 3) showed the titres of H-I antibodies and neutralizing antibodies in the sera not to be closely correlated. The H-I antibodies found in reciprocal titres of 20 to 40 in sera with undetectable titres of neutralizing antibodies are explained by non-specific inhibitors against the haemagglutinin, which has been reported earlier (13). On the other hand, these inhibitors offer no explanation for the absence of H-I antibodies in sera with high titres of neutralizing antibodies. Although the neutralization test must, theoretically, be more sensitive than the H-I test, this seems to suggest a lack of identity between the two types of antibodies demonstrated by these tests.

A lack of identity between H-I and neutralizing antibodies against influenza viruses has been observed earlier (17, 19). It was shown that on adsorption of immune sera with live influenza viruses the neutralizing antibodies were reduced to a significantly greater extent than the H-I antibodies (19). It has also been found that some strains of U-virus showed low titres of haemagglutinin, and immune sera prepared against these strains gave neutralizing antibodies but no H-I antibodies against the homologous strain (12).

A difference in serologic response measured by H-I and neutralization tests was also noticed in the croup children. Thus, H-I antibodies above 40 in reciprocal titre were present in 82.8 per cent of the convalescent sera from the Croup children compared with 32.8 per cent for neutralizing antibodies at or above 2 in reciprocal titre. An earlier rise in H-I antibody titres than in neutralizing antibody titres in sera obtained after immunization has been shown for influenza virus (17) and similar results have been presented concerning the U-virus in transmission experiments (15). Thus, the intervals of time used in this study between the acute phase and the convalescent sera may have favoured the appearance of H-I antibodies.

Cortisone may involve an impaired response in neutralizing antibodies (7, 8). The patients treated with prednisone showed significant increases in neutralizing antibodies in 11.6 per cent, although viruses were isolated in 32.5 per cent of these cases. Corresponding values for the non-treated were 45 per cent for increase in neutralizing antibodies and 40 per cent for

virus isolations. It should also be noted that longer intervals between acute-phase and convalescent sera were used in more of the cases treated with prednisone than in the non-treated cases. It would appear, then, that the prednisone treatment may involve an impaired response in neutralizing antibodies in this study.

The role of the U-virus in the aetiology of non-diphtheritic croup chiefly of subglottic type is difficult to evaluate. The virus was isolated from throat and/or faecal specimens in 30 per cent of the 87 admittances of this disease investigated. Further, a significant increase in titre between the two serum specimens was recorded in 24 per cent for H-I antibodies, in 22 per cent for neutralizing antibodies, and in 38 per cent in either test. Thus, it seems reasonable to assume that in 38 per cent of the cases studied, U-virus infection had occurred during the period of croup manifestations. In conclusion, the results of virus isolation attempts and the serological investigation showed the U-virus to be associated with croup in about 38 per cent of the 87 cases investigated. Further, it was found that 4 out of 21 children showed non-diphtheritic croup in an epidemic of upper respiratory disease studied separately and associated with U-virus (14).

Although the pathogenesis of non-diphtheritic croup of subglottic type is still obscure, evidence has been presented (10, 16) suggesting bacteria to be of minor importance as the precipitating agent in most cases. Further some virologic evidence has been presented for the association with the disease of influenza viruses (4, 9), CA-virus (1) and now U-virus.

Results have previously been arrived at suggesting a non-infectious factor to be present in the pathogenesis of this disease; it was shown that the incidence of croup was higher in families in which one of the children had suffered from croup than in control families (11). An allergic factor in the croup syndrome has been proposed, although sparse evidence has been presented (6, 18). A high percentage of non-diphtheritic croup has been observed in cases developing asthma of an infectious allergic type (2). This accumulated evidence seems to justify the assumption that non-diphtheritic croup of subglottic type may be attributed to an allergic manifestation in which the sensitizing agent may be common upper respiratory viruses in most cases.

Summary

A virologic investigation of 87 non-diphtheritic croup cases of subglottic type, including virus isolations from throat and faeces in tissue cultures and investigation of paired sera from the children, is presented. The clinical data of 34 cases were analyzed. A group of children from Day-Nurseries (67 Nursery children) and a control group from the Out-Patient Department of the Surgical Department (20 Casualty children) were

investigated simultaneously. Only one serum specimen was taken from the last two groups of children. Thirty per cent of the Croup children had positive isolates of a recently isolated virus called U-virus in throat and/or faeces. The corresponding frequencies for the Nursery and Casualty children were 12 and 0 per cent respectively. The serologic investigation showed neutralizing antibodies in 30 per cent, and haemagglutination-inhibiting antibodies in 20 per cent of the sera of the Nursery children. Among the Casualty children, no specific antibodies were recorded.

The Croup children showed H-I antibodies in 82.8 per cent and neutralizing antibodies in 32.8 per cent of the convalescent sera. Significant rises between paired sera were recorded in 24 per cent for H-I antibodies, in 22 per cent for neutralizing antibodies, and in 38 per cent in either test. The possible role of prednisone treatment in the poor serologic response in neutralizing antibodies, and the pathogenesis of the non-diphtheritic croup syndrome of the subglottic type, are discussed. The accumulated evidence concerning this disease suggests an infectious factor probably of a viral nature and a non-infectious factor, the nature of which is still undetermined, to be involved in the pathogenesis.

Etiologie du croup non-diphtérique. II. Investigation virologique.

On présente une investigation virologique de 87 cas de croup non-diphtérique du type subglottique, y compris les isolements de virus provenant de la gorge et des excréments dans les cultures tissulaires, et une investigation de sérums combinés provenant d'enfants. Les données cliniques de 34 cas furent analysées. On a examiné simultanément un groupe d'enfants de crèches (67 enfants en nourrice) et un groupe de contrôle provenant de la polyclinique du Service de Chirurgie (20 enfants casuels). On n'a prélevé qu'un seul spécimen de sérum sur les deux derniers groupes d'enfants. 30% des enfants ayant le croup avaient des isolements positifs d'un virus isolé récemment, appelé le virus U, dans la gorge et/ou les excréments. Les fréquences correspondantes pour les enfants des crèches et les enfants casuels étaient de 12%, respectivement 0%. L'investigation sérologique montra des anticorps neutralisants dans 30%, et des anticorps inhibant l'hémagglutation dans 20% des sérums des enfants de crèches. Parmi les enfants casuels, on n'a pas signalé d'anticorps spécifique.

Les enfants ayant le croup montrèrent des anticorps inhibant l'hémagglutination dans 82,8% et des anticorps neutralisants dans 32,8% des sérums convalescents. Des augmentations signifiantes parmi les sérums combinés étaient signalées dans 24% pour les anticorps inhibant l'hémagglutination, 22% pour les anticorps neutralisants et 38% dans chaque test. On discute le rôle possible d'un traitement à la prednisone vis-à-vis de la réponse sérologique faible dans les anticorps neutralisants, et la pathogénèse du syndrome de croup non-diphtérique du type subglottique. L'évidence accumulée concernant cette maladie fait penser à un facteur infectieux, probablement de nature virulente, et un facteur non-infectieux dont la nature n'est toujours pas déterminé, à impliquer dans la pathogénèse.

Ätiologie nicht-diphterischen Krupps. II. Virologische Untersuchung.

Vorliegend eine virologische Untersuchung, die 87 nicht-diphterische Krupp-Fälle des Subglottis-Typs, Virusisolationen aus Rachen und Faeces in Gewebskulturen sowie Untersuchung paarweiser Seren der Kinder betrifft. Die klinischen Data von 34 Fällen wurden analysiert. Es wurden eine Gruppe Kinder aus Tages-Kinderheimen („Day nurseries": 67 Kinder) und eine Kontrollgruppe vom „Out-patient Depart-

ment of the Surgical Department" (20 chirurgische Kinder) gleichzeitig untersucht. Nur eine Serum-Probe wurde von den letzten 2 Gruppen der Kinder genommen. 30% der Krupp-Kinder gaben positive Isolationen eines unlängst isolierten Virus, genannt U-Virus, in Rachen und/oder Faeces. Die entsprechende Häufigkeit des Auftretens bei den Tagesheimkindern und den chirurgischen Kindern betrug 12 bzw. 0%. Die serologische Untersuchung ergab in 30% neutralisierende Antikörper und in 20% Blutagglutinationshemmende Antikörper der Sera der Tagesheimkinder. Unter den chirurgischen Kindern fand man keine spezifischen Antikörper.

Die Krupp-Kinder wiesen in 82,8% der Konvalescentensera blutagglutinationshemmende Antikörper und in 32,8% neutralisierende Antikörper auf. Eine signifikante Zunahme der Werte zwischen den gepaarten Seren wurde in 24% für die blutagglutinationshemmenden Antikörper und in 22% für die neutralisierenden Antikörper gefunden, in 38% in jedem von beiden Testen. Der mögliche Einfluss einer Prednison-Behandlung auf die spärliche serologische Reaktion betreffend die neutralisierenden Antikörper und die Pathogenese der nicht-dipterischen Krupp-Syndrome des Subglottistyps werden diskutiert. Die Häufigkeit der Beweise bezüglich dieser Krankheit legt es nahe, einen infektiösen Faktor — wahrscheinlich eine Virusart — und einen nicht-infektiösen Faktor, dessen Natur noch nicht geklärt ist, in die Pathogenese aufzunehmen.

Etiología del crup no diftérico. II. Investigación virológica.

Se exponen los resultados de la investigación virológica de 87 casos de crup no diftérico de tipo subglótico, que comprende la aislación del virus de la faringe y heces en los cultivos de tejidos y la investigación de suero homólogo de los niños. Se analizaron los sintomas clínicos de 34 casos. Fueron objeto de una investigación simultánea un grupo de niños pertenecientes a los pabellones de lactantes (67 niños) y un grupo control del Ambulatorio del Departamento de Circugía (20 niños tomados al azar). De los dos grupos de niños solo se tomó una muestra de suero. El 30 por ciento de los niños afectos de crup poseian en sus fauces o heces virus U, aislado recientemente. Las frecuencias correspondientes a los niños del Pabellón de lactantes y los niños tomados al azar fueron de 12 y 0 respectivamente. El estudio serológico demostró la existencia de anticuerpos neutralizantes en el 30 por ciento de los sueros de los niños pertenecientes al Pabellón de lactantes, y anticuerpos inhibidores de la hemaglutinación de lactantes, y anticuerpos inhibidores de la hemaglutinación en el 20 por ciento. En los niños tomados al azar no se hallaron anticuerpos específicos.

Los niños afectos de crup presentaron anticuerpos H-I en el 82 por ciento de los casos, y anticuerpos neutralizantes en el 32,8 por ciento de los sueros de convalecientes. Aumentos significativos de los sueros homólogos se registraron: en el 24 por ciento para los anticuerpos H-I, en el 22 por ciento para los anticuerpos neutralizantes, y el 38 por ciento en otras pruebas. Se discuten la posible significación del tratamiento con prednisona en la pobre respuesta serológica en anticuerpos neutralizantes y la patogenia del sindrome crupal no diftérico de tipo subglótico. Las distintas observaciones concernientes a esta enfermedad inducen a pensar en un factor infeccioso, probablemente de índole vírica y un factor no infeccioso, desconocido, en la patogenia del proceso.

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Prothrombin Determination in Infants: A Comparison of the Methods of Quick–Lehmann and Owren

by K. B. BJÖRNESJÖ and FRITZ KARLSTRÖM

Owren in 1949 published a new method for prothrombin determination which had certain advantages over methods used earlier. The method required a rather large quantity of blood, and was therefore not practicable for prothrombin determination in infants. In 1954, however, Dyggve & Lund published a micro-modification of Owren's method, and subsequently other micro-modifications have been reported(Rosling & Schoenheyder, 1955; Sundblad, 1955).

The aim of this investigation is a comparison of Quick–Lehmann's micro-method and Sundblad's modification of Owren's method.

In analysing coagulation factors the principle is that all these factors, except that which is to be determined, are added in excess to the plasma which is to be analysed. The coagulation time for the interreaction can then be used as a measure for the factor being investigated. In order that coagulation shall take place, active thromboplastin, prothrombin, fibrinogen and calcium are required. The newly-discovered coagulation factors proaccelerin (Factor V) and proconvertin (Factor VII) are also necessary for coagulation. In Quick–Lehmann's method, thromboplastin and calcium are added in excess to the blood sample. The coagulation time in this system is then not only influenced by the prothrombin but also by the proportion of fibrinogen, proaccelerin and proconvertin contents in the investigated blood. The proaccelerin is labile and is rapidly destroyed when the blood samples are allowed to stand, therefore the analysis according to Quick-Lehmann's method must be performed quickly after taking the blood. Otherwise a reduction in the proaccelerin content can affect the coagulation time. In order to avoid an effect on the determination by variations in the plasma fibrinogen and proaccelerin content, Owren worked with plasma diluted 1 : 10, and added as a source of fibrinogen and proaccelerin, oxplasma, from which prothrombin and proconvertin had been removed by means of

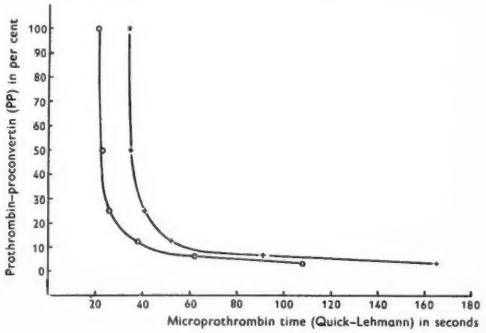

Fig. 1. Relation between PP-value and prothrombin time. ×——×, a commercial thromboplastin reagent (Idokinas Ferrosan); O——O, a thromboplastin reagent prepared according to Owren in our laboratory.

filtration through an asbestos filter. In this way an excess of fibrinogen and proaccelerin are ensued in the reaction mixture. In Owren's routine method the combined effect of prothrombin and proconvertin is consequently determined. To indicate this, Owren has called the method the P & P method. Proconvertin is a coagulation factor which has close relation to prothrombin. Like prothrombin, it is produced in the liver under influence of vitamin K, and is reduced in liver injury and in anticoagulation treatment with dicumarol preparations. A method which estimates both these factors at the same time is therefore very useful as a liver function test and in control of dicumarol treatment.

Another difference between Quick–Lehmann's and Owren's methods is the terms of reference in which the result is indicated. As the coagulation time after addition of calcium to the plasma can vary greatly with different thromboplastin reagents in one and the same plasma, the coagulation time alone is no true measure of the prothrombin quantity of the sample. The coagulation time must be compared with that of a normal plasma determined with the same reagents as the sample. Lehmann has chosen to do this by

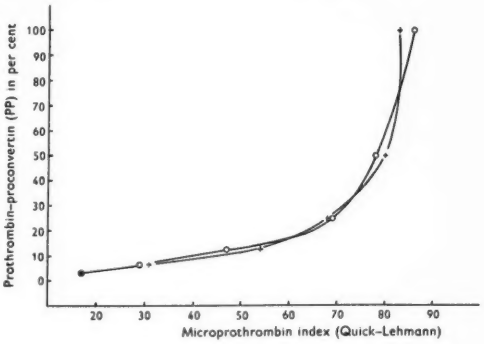

Fig. 2. Relation between PP-value and prothrombin index. ×——×, a commercial thromboplastin reagent (Idokinas Ferrosan); O——O, a thromboplastin reagent prepared according to Owren in our laboratory.

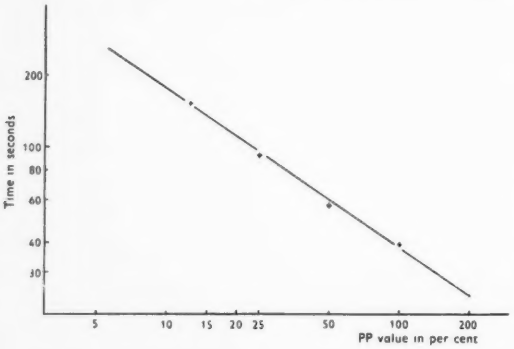

Fig. 3. Correlation graph for prothrombin-proconvertin (PP). This graph has been prepared by coagulation time determinations for various dilutions of normal blood containing 100% prothrombin-proconvertin. The figures are plotted on double logarithmic paper.

giving the result in the form of a prothrombin index, i.e. the coagulation time for normal plasma divided by the coagulation time for the sample, after which the quotient is multiplied by 100. It is seen by Figs. 1 and 2 that the prothrombin index is influenced by the differences in the thromboplastin reagent to a very much lesser degree than the coagulation time. In Owren's method the value in percentage of normal value is indicated by means of a correlation graph drawn by plotting the coagulation times of various dilutions of some normal plasma samples on double logarithmic paper (Fig. 3). The mean coagulation time for normal plasma diluted 1:10 is fixed at 100%. This method of calculation gives a better quantitative measurement of the prothrombin content than prothrombin index.

Earlier, comprehensive investigations of the prothrombin content in infant blood have been made by Plum (1949) and Dyggve (1952). It was shown that the prothrombin content in children who had not received vitamin K was lowered at birth, and that the prothrombin values were further reduced during the course of the succeeding days, to reach a minimum on the third day. After this the values rose again and by the 7th day reached the birth level.

Our own first series of experiments comprised 40 new-born infants, on which prothrombin determinations were performed both during the 1st and the 3rd–4th days. All the children in this series received vitamin K prophylaxis according to the following scheme: The expectant mother, on admission to the hospital, received 3 tablets vitamin K (each tablet containing 10 mg menadiol-tetrasodium-diphosphate), and the child received in addition ½ ml vitamin K (5 mg menadiol-tetrasodium-diphosphate) intramuscularly, if it was born within 6 hours of the time when the mother received her tablets. If the delivery did not take place within 48 hours after admission, the mother then received one 10 mg tablet of vitamin K

TABLE 1

The relation between Prothrombin index (Quick–Lehmann) and PP-value (Owren) in new-born children.

Time	No. of individuals	Prothrombin index		PP-value (%)	
		Mean	Range	Mean	Range
0–1 day after delivery	40	67	15–95	27	<5–53
3–4 days after delivery	40	73	14–105	35	<5–66

every day. On all the children in this experimental series parallel determinations were made with Quick–Lehmann's and Owren's methods. The results are shown in Table 1. The reduction in the prothrombin-proconvertin content is considerably more marked according to Owren's method. The lowering in the prothrombin value during the first days of life, pointed out by Plum, is not apparent in our material. This difference is probably due to the fact that the children in our experiments, as opposed to those of Plum's, received vitamin K prophylaxis. The relatively slight reduction in the prothrombin index in relation to the PP-values is dependent on the lack of sensitivity in the Quick–Lehmann method to moderate lowerings in the prothrombin level, which is clearly shown by Figs. 1 and 2. A lowering of the prothrombin level to 50% of the normal only insignificantly affects the prothrombin time and prothrombin index, according to Quick–Lehmann. On the other hand the PP-values according to Owren appear to be surprisingly low.

It is important in this connection to investigate the significance of the

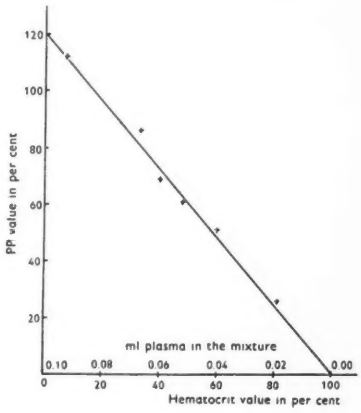

Fig. 4. Relation between hematocrit and PP-value (Sundblad) in mixtures of plasma and blood corpuscles in various proportions.

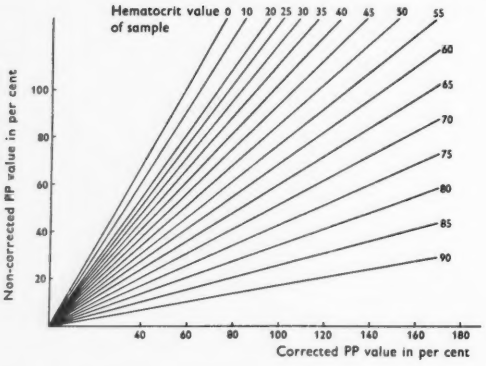
Hematocrit value of sample
0 10 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90
Non-corrected PP value in per cent
20 40 60 80 100
40 60 80 100 120 140 160 180
Corrected PP value in per cent

Fig. 5. Nomogram for correction of PP-values to a hematocrit of 42 %.

hematocrit variations. With the micro-method, which is carried out on whole blood, it is evident that a smaller quantity of plasma is present in the reaction mixture at a high hematocrit value than with a low hematocrit value, and this must influence the result. In order to throw light on the effect of the hematocrit value, the following experiment was performed, using a plasma with a known prothrombin content, to which packed red cells were added in varying proportions. On all the mixtures hematocrit determinations and micro-prothrombin determination according to Sundblad were performed. For hematocrit determination blood was taken in heparinised capillary tubes, which were centrifuged in an International Micro-Hematocrit-Centrifuge for 5 minutes at a speed of 11,000 rev./min. The result is shown by Fig. 4. There is a rectilinear relation between the PP-value, hematocrit value and plasma volume in the coagulation mixture. The rectilinear course of the curve means that a correction factor for variations in the hematocrit values can easily be calculated. The correction factor with which the PP-value found, should be multiplied in order to be corrected to a normal hematocrit value is $(100 - Hn)/(100 - H)$,[1] where Hn represents the normal mean value for hematocrit, and H the hematocrit value for the actual sample. The correction can also be easily carried out with a nomogram worked out with the help of the above-named factor (Fig. 5).

In another experimental series, hematocrit and PP-determinations were made simultaneously in different age groups, and at the same time the values were corrected to a hematocrit value of 42 %, which is the mean hematocrit value for our material from healthy adults. The blood samples in this series have been taken from healthy children in connection with routine health investigations. The result is represented in Table 2. The

[1] This formula can be used generally for correction to a normal mean hematocrit value when analysis of substances found in plasma but not in cells are carried out on whole blood.

TABLE 2

Prothrombin-Proconvertin (PP-value) in plasma of children and adults.

Age group	No. of individuals	% hematocrit, mean	Non-corrected PP-value (%), mean	Corrected PP-value (%)		
				Mean	S.D.	Error of the mean
0–1 day	30	70	33	65	15.8	2.9
1–3 mo.	30	42	77	77	13.8	2.5
3–6 mo.	30	39	88	84	18.1	3.3
6–9 mo.	30	38	98	92	12.9	2.4
9–12 mo.	30	39	99	93	11.1	2.0
1–6 yrs.	30	39	105	100	16.3	3.0
Adults	30	42	100	100	17.5	3.2

table shows that the high hematocrit values in the new-born give approximately 50% too low PP-values. The mean hematocrit value (70%) in our material of new-born infants is remarkably high. (Several investigators give the values as between 55–65%.) This value has, however, been obtained from the same blood which was used for the prothrombin determination, so the correction must be based on this value. Our hematocrit values for adults correspond, on the other hand, with the values which are given in the literature, and therefore it seems improbable that our high hematocrit values in the new-born should be due to a technical error during the hematocrit determination. Table 2 further shows that the error caused by the hematocrit variations for healthy infants over the age of one month is insignificant. The PP-values increase continuously during the first year of life to reach the same level as in the adult.

It has been discussed whether the low prothrombin values in infants during the neo-natal period are due to a vitamin K deficiency or to a lowered ability of the liver to synthesize prothrombin and proconvertin. Before vitamin K prophylaxis came into use, vitamin K deficiency played a large part, but such prophylaxis is practised now in most maternity departments. In order to obtain an idea of whether a vitamin K deficiency exists in our material, 10 new-born infants were chosen with varying PP-values, and these infants received, over and above the usual vitamin K prophylaxis, ½ ml vitamin K intramuscularly. The PP-values in the infants in this group were determined both at the beginning of the experiment and after 2 and 4 days. All the values were corrected to a hematocrit value of 42%. The PP-values increased in all the infants investigated, but the increase varied considerably from case to case, which is shown by Fig. 6. The average increase was 43% of the initial value. This figure is unex-

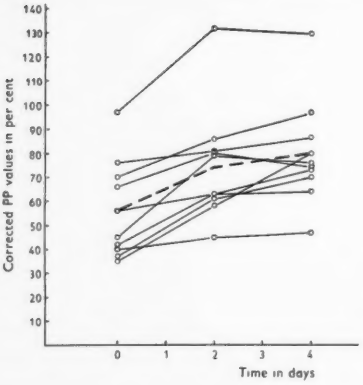

Fig. 6. Effect of vitamin K on PP-values, ½ ml K-vimin = 5 mg menadiol-tetrasodium-diphosphate has been given in intramuscular injection immediately after taking the first specimen for PP analysis. The line of short dashes indicates mean values.

pectedly high, and suggests that a vitamin K deficiency may exist in at least some of the infants in this group. A certain increase in the prothrombin-proconvertin values after vitamin K injection is also obtained, however, in liver injury without lack of vitamin K, but the increase is not so large as in the case of vitamin K deficiency. The fact that the prothrombin-proconvertin values do not reach the adult level until the end of the first year of life supports the idea that there probably also exists a reduced capacity of the liver, not due to vitamin K deficiency, to produce these coagulation factors during the first year of life. In this respect there is an analogy with gamma-globulin, which gradually increases during the first year of life to the same level as in the adult.

Summary

A series of prothrombin determinations have been carried out on infants, partly according to Quick–Lehmann's micro-method and partly according to Sundblad's micro-modification of Owren's method. The significance of the hematocrit variations has been investigated, and a formula for the correction of the prothrombin values to a normal mean hematocrit value is given.

Owren's method is superior to Quick–Lehmann's method for the detection of small reductions in the prothrombin-proconvertin content, and is therefore useful as a sensitive liver function test, which is not the case in Quick–Lehmann's method. Owren's method also facilitates a simple correction with regard to variations in the hematocrit value. Such a correction is necessary in order to obtain an exact value in prothrombin determination in infants in the neo-natal period, and this should be carried out even in older children in those cases where the hematocrit value deviates considerably from the normal.

Dosage de la prothrombine chez les nourrissons : une comparaison entre la méthode de Quick–Lehmann et celle de Owren.

On a effectué chez les nourrissons une série de dosages de la prothrombine, en partie selon la micro-méthode de Quick–Lehmann, et en partie selon la micro-modification de

Sundblad de la méthode de Owren. L'importance des variations de l'hématocrite a été examinée et une formule a été donnée pour la correction des valeurs de prothrombine afin d'obtenir une valeur moyenne normale de l'hématocrite.

La méthode de Owren est supérieure à celle de Quick–Lehmann pour détecter les petites réductions dans la teneur en prothrombine/proconvertine. Elle est pour cette raison utilisable et tant que test sensible du fonctionnement du foie, ce qui n'est pas le cas avec la méthode de Quick–Lehmann. La technique de Owren facilite également une simple correction en ce qui concerne les variations dans la valeur de l'hématocrite. Une telle correction est nécessaire pour obtenir une valeur exacte dans le dosage de la prothrombine chez les nourrissons pendant la période néonatale. Elle devrait être effectuée même chez les enfants plus âgés, et ceci dans les cas où la valeur de l'hématocrite diffère considérablement de la valeur normale.

Prothrombinbestimmung bei Kindern. Ein Vergleich zwischen der Methoden Quick–Lehmann und Owren.

Es wurde eine Serie Prothrombinbestimmungen bei Kindern durchgeführt, zum Teil nach der Quick–Lehmannschen Mikromethode und teilweise nach der Sundbladschen Mikromodifikation oder Owrenschen Methode. Die Wichtigkeit der Hämatokritvariationen wurde untersucht und eine Formel für die Berichtigung der Prothrombinwerte gegenüber einem normalen Durchschnittswert wird gegeben.

Die Owrensche Methode ist der von Quick–Lehmann hinsichtlich der Aufdeckung von kleinen Minderungen des Prothrombin-Proconvertin-Gehaltes überlegen und ist insofern als empfindlicher Leberfunktionstest nützlich, was von der Methode laut Quick–Lehmann nicht gesagt werden kann. Owrens Methode erleichtert auch eine einfache Korrektion bezüglich der Variationen des Hämatokritwertes. Eine derartige Korrektion ist nötig, um einen exakten Wert bei der Prothrombinbestimmung bei Kindern, besonders in der neo-natal-Periode, zu erhalten. Es lässt sich dies auch bei älteren Kindern durchführen und ist in Fällen, wo der Hämatokritwert beträchtlich vom normalen Werte abweicht, sicher anzuraten.

Determinación de la protrombina en los niños: Comparación entre los métodos de Quick–Lehmann y Owren.

Se han llevado a cabo una serie de determinaciones de la protrombina en niños, en parte según el micrométodo de Quick–Lehmann, y en parte mediante la micromodificación de Sundblad del método de Owren. Se han investigado los valores del hematocrito, dándose una fórmula para la corrección de los valores de la protrombina para un valor hematocrito normal.

El método de Owren es superior al de Quick–Lehmann para la detección de pequeñas disminuciones del índice protrombina-proconvertina, por lo que puede utilizarse como prueba sensible del funcionalismo hepático, lo que no ocurre con el método de Quick–Lehmann. El método de Owren facilita también una corrección simple en relación a las variaciones del valor hematocrito. Esta corrección es necesaria a fin de obtener una cifra exacta en la determinación de la protrombina en los niños en el periodo neonatal, debiendo ser llevada a cabo incluso en niños mayores, en los casos en que el valor hematocrito se desvía considerablemente del normal.

Acknowledgements

We are indebted to Mrs. I. Jansson who has performed the prothrombin determinations throughout the work and to Miss Ulla-Brita Chöler for collecting of blood samples.

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Renal Concentration Capacity during Acute, Nonobstructive Urinary Tract Infections in Infancy and Early Childhood

by JAN WINBERG

Renal function during acute, uncomplicated, urinary tract infections has received only little interest. This is perhaps due to the fact that the clinical symptoms and routine urine and blood examinations as a rule do not indicate any marked interference with renal function. There are, however, some observations suggesting an impaired renal conservation of water.

Craig (1935) noted that intense thirst is common during neonatal pyelonephritis even after subsidence of fever, although the symptom seems hard to recognize with any certainty at that age. The same author mentions also polyuria as a symptom, but no figures are given. A marked weight instability is often seen during the acute stage of infantile urinary tract infections, but it is doubtful whether this depends upon gastrointestinal loss or impaired renal function. There are, however, some reports which suggest that infections of the urinary tract may cause damage to the part of the nephron responsible for the renal water economy. Thus, Longcope & Winkenwerder (1933) and Brod (1956) has stated that a decreased concentration capacity with retained dilution ability is the typical finding in chronic pyelonephritis and Linneweh (1957) has demonstrated decreased specific gravity of urine in one case of acute pyelonephritis in a child, who, however, exhibited a marked non-protein nitrogen retention.

The present investigation was undertaken to test the ability of the kidney to conserve water during and after acute, febrile, nonobstructive urinary tract infections in infancy. It was felt to be of value to establish whether there were any such signs of renal damage in this disease, so often classified as simple cysto-pyelitis. The results give evidence of a defect of the renal concentration capacity, which may persist after the clinical symptoms of infection have disappeared.

Material

The material consists of six consecutive cases of acute, febrile, urinary tract infection admitted to the clinic. The general condition was good in all, the reason for admission being diarrhoea or fever of unknown origin. In all cases it was the first

Fig. 1. Case 4. K. S. 570702. Girl aged 6 months. Urethrocystography during the 2nd week of an acute pyelonephritis. Note refluxes to both ureters and pelvices during micturition. No obstruction of urethra. On control 7 weeks later normal findings.

infection observed, all were uncomplicated by malformations of the urinary tract. The diagnosis was settled by positive urine cultures and the demonstration of an increased number of leucocytes in the urinary sediment, examined after centrifuging urine in the ordinary clinical centrifuge for about five minutes. In the female, urine was obtained for culture and sediment investigation by bladder catheterization. In the male, urine was collected after thorough cleaning of the penile foreskin, glans and urethral orifice. In no case was there any signs of balanitis.

Intravenous urography was performed in all cases, in some showing infectious irritation of the pelvices and ureters, but otherwise demonstrating normal anatomical conditions. Micturition urethrocystography as described by Kjellberg, Ericsson & Ruthe (1957) was also performed in all cases. There was no obstruction of the urinary stream, but there was reflux to ureters and pelvices in four cases, see Table 1 and Fig 1.

The chemotherapeutic doses used have been of the same magnitude as those administered in pneumonia. For further clinical details see Fig. 2–7.

TABLE 1

Uretero-pelvic reflux observed in micturition urethrocystography.

Case	Sex	Uretero-pelvic reflux		
		Bilateral	Unilateral	No reflux
1	Female		+	
2	Female			+
3	Male		+	
4	Female	+		
5	Male			+
6	Female	+		

Procedure

The renal concentration capacity was determined in the following manner in Cases 3–6. At 4 p.m. pitressin tannate in oil (Parke & Davis) was administered intramuscularly at a dose of about 0.5 pressure units per 6 kg of body weight. The ampoules were warmed in the hand and well shaken before administration. The injection was given by a tuberculin syringe with 1/100 ml graduations. To ensure an accurate dosage care was taken to fill the injection needle with pitressin before the injection was made. Fluids were withdrawn from 6 p.m. the day of injection, until the second urine specimen was obtained (see below). Thus the patients were deprived of water for between 15 and 16 hours. No such test was performed during a febrile stage.

As a rule urine was collected between 8 p.m. the day of injection until 8 a.m. the next day. The patients were thoroughly observed to void between 6 and 8 o'clock in the morning. Another urine specimen was obtained usually between 9 and 10 o'clock

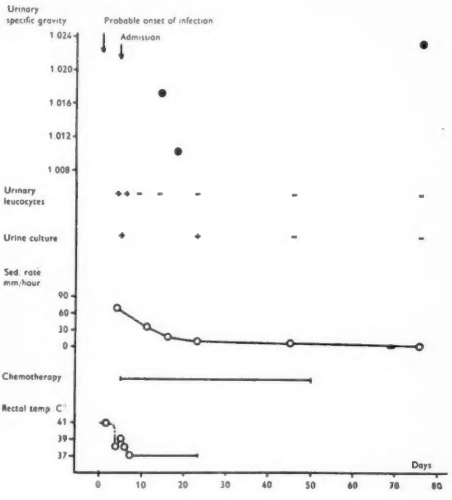

Fig. 2. Case 1. M. M. 561126. Girl aged 12 months. First attack of acute pyelonephritis. ● indicates concentration of urine after 18 hours of water deprivation. There is a definite depression of the concentration capacity shortly after the subsidence of the acute symptoms. The last filled circle corresponded to an osmolal concentration of 987 mOsm./l. Dilution capacity determined 19 days after onset of the disease 1.002.

in the morning. To prevent evaporation the second urine specimen, within 15 minutes after voiding, was put into a test tube and stoppered.

In Cases 1 and 2 no pitressin tannate was given, but the patients had fluids withheld for 18 and 17 hours respectively.

The concentration capacity determined in these experiments is not definitely the maximal one. According to Miles, Paton & de Wardener (1954), this is not arrived at with any reliability until after 22 hours of water deprivation, at least in adults. No experiments defining the time of water deprivation required to establish maximal urinary concentration in infants seem to have been performed, but from the investigation of Pratt, Bienvenu & Whyte it seems probable, at any rate, that this time is not longer than that in adults.

The administration of pitressin serves two functions. The first is to diminish the risk of such spontaneous diuresis as described by Hart & Verney (1934) during progressive dehydration. Further as demonstrated by Miles *et. al.* the administration of pitressin tannate in oil without simultaneous water restriction to patients with renal disease gives a fairly reliable estimation of the maximal concentration capacity.

It is anticipated that when 15–16 hours' water deprivation is combined with administration of pitressin tannate as in the present study, this procedure, although perhaps not establishing the maximal concentration capacity, gives a good conception of the renal ability to conserve water.

Dilution capacity of the kidneys was tested in Cases 1, 2, 4 and 5 after a water load. In Cases 3 and 6 the specific gravity of the 24-hour urine specimen was so low as to make a dilution test unnecessary.

Methods

The osmolality of urine was calculated from the freezing point depression determined with the aid of a thermistor and a Wheatstone's bridge. With the apparatus used the osmolality is determined with an accuracy of ± 5 mOsm./l.[1]

Specific gravity was determined by weighing.

Results

The results are summarized in Figs. 2–7.

In Case 2 (Fig. 3) the concentration capacity was good when determined approximately 2 weeks after the probable onset of the disease. The signs and symptoms in this case were very mild.

In the rest of the cases one or several of the urinary solute concentrations observed 2–3 weeks after the onset of infection were lower than even the lowest concentration seen in a series of infants without kidney disease (to be published, Winberg, 1959, a). Eight to twelve weeks after subsidence of the acute symptoms of infection the urine solute concentrations observed had all returned to the normal range.

[1] The author is greatly indebted to Dr. J. Bergström, Department of Clinical Chemistry, S:t Eriks Hospital, Stockholm, for the performance of the determinations of the freezing point depression.

In Case 3 (Fig. 4) the first concentration test was performed 6 days after the probable onset of infection, and urinary solute concentration was then found to be relatively high. During the second and third week urine solute concentrations lower than the normal were observed.

In Cases 4 and 5 (Figs. 5 and 6) the clinical state of the patients precluded performance of concentration tests as early as in Case 3. This might explain the fact that the lowest concentrations seen in these cases were already observed during the first test. In Case 5 intravenous urography performed at two different occasions, showed marked inflammatory irritation on the right side, but none on the left. This might possibly indicate a unilateral infection and explain why the lowest urine solute concentration observed in this case was not as low as that in the others.

In Case 6 the urine volumes some days amounted to as much as 700–800 ml per 24 hours with fluid intake of 1000–1100 ml. The patient was very irritable with a fluid intake of less than 1000 ml daily, although her weight was only 4000 grams. The first two solute concentrations were obtained without true water deprivation. Even so, the results shown in Figure 7, combined with the excessive 24 hour urine volumes were suggestive of a defect in water economy. In this case decreased urine solute concentration was again observed during a reactivation of infection.

In Case 1, which was not given pitressin, the lowest specific gravity

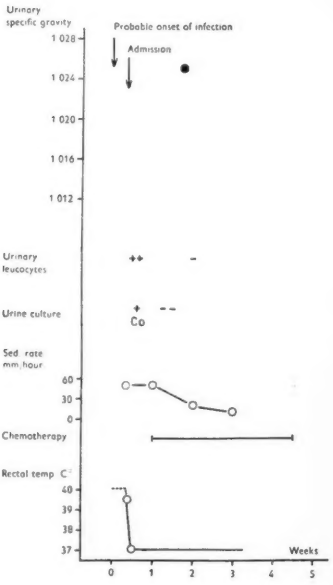

Fig. 3. Case 2. C. W. 560228. Girl aged 20 months. First attack of acute urinary tract infection. ● indicates concentration of urine after 17 hours of water deprivation. Colon bacilli cultured from urine, completely resistant to sulfa. Sterile urine 2 days after inadvertent administration of sulfisoxazole (gantrisin) might suggest a very limited infection. In this case there was no depression of the concentration capacity. Dilution capacity 1.002. *Co* = E. coli.

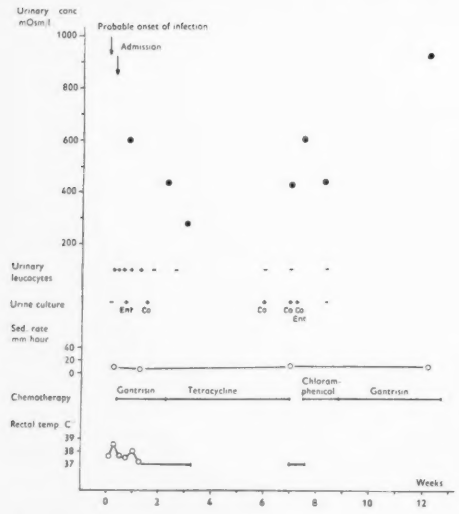

Fig. 4. Case 3. L. P. 570810. Boy aged 4 months. First attack of acute pyelonephritis. ● indicates concentration of urine in antidiuresis (see Procedure). The successive decrease in urinary concentration might reflect increasing renal damage. Note that sedimentation rate is normal throughout and no pus cells are found from the second week, although there is impaired renal function. The general condition was good. Specific gravity of 24-hour urine sample 1.003–1.005 during the 2nd and 3rd week. *Co* = E. coli; *Ent* = Enterococci.

observed was considerably lower than that observed by Marquardsen & Jochims (1957)[1] after water deprivation but without pitressin administration in normal cases.

When the urine concentrations observed in this case are evaluated it has to be remembered that specific gravity is a very unreliable guide to osmolal concentration of urine. The author found that thirteen urine specimens

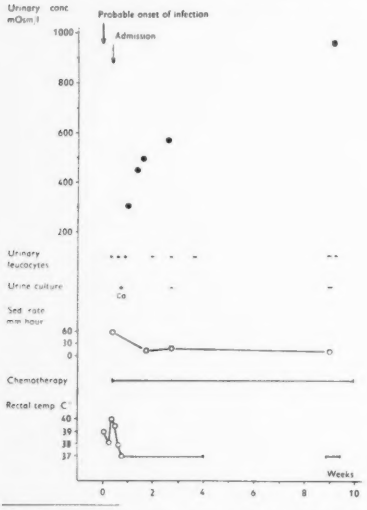

Fig. 5. Case 4. K. S. 570702. Girl aged 6 months. First attack of acute pyelonephritis. ● see Fig. 4. There is a marked depression of concentration capacity during the first weeks after onset of infection. Dilution capacity during the 3rd week 116 mOsm./l. *Co* = E. coli.

[1] Marquardsen, G. und Jochims, J.: Arch. Kinderheilk. *156*: 34, 1957.

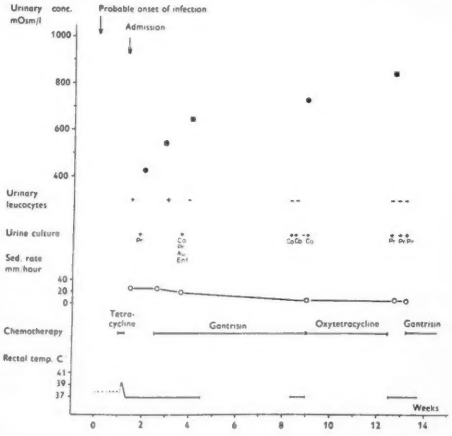

Fig. 6. Case 5. J. J. 570901. Boy aged 4 months. First attack of acute pyelonephritis, possibly unilateral. ● see Fig. 4. There is a low urine concentration 2–3 weeks after the onset of disease. Osmolal concentrations of urine within normal range is achieved between 4 and 9 weeks after onset, although the infection persists in a subchronic stage. I.v. urography 14 weeks after onset shows evidence of infection. Dilution capacity determined during the 3rd week 80 mOsm/l. *Co* = E. coli; *Pr* Proteus vulgaris; *Au* = Staph. aureus; *Ent* = Enterococci.

from different persons showing a specific gravity of 1.010 had osmolal concentrations varying between 255 and 418 mOsm./l. and that 10 specimens with a specific gravity of 1.017 showed osmolal concentrations varying between 472–685 mOsm./l.

Endogenous creatinine clearance was markedly lowered during the acute stage of the disease only in Case 6 (to be published, Winberg, 1959, b). The renal acidification mechanism was tested and judged to be normal, all cases reaching a urinary pH of 4.91 or less.

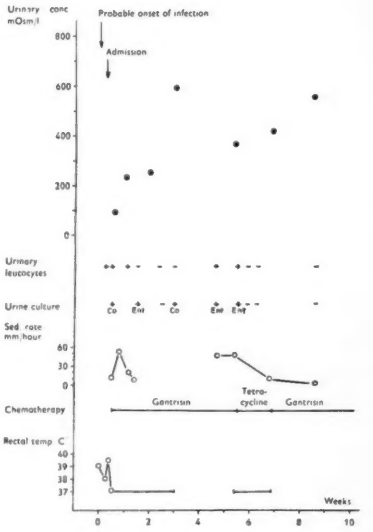

Fig. 7. Case 6. I. B. 571220. Girl aged 6 weeks. First attack of acute pyelonephritis. ● see Fig. 4. Because this patient initially showed symptoms of intense thirst, and had 24 hours urine output of between 7–800 ml, fluids were withheld for a shorter time than in the other patients. Pitressin tannate was administered as described earlier. Duration of fluid deprivation:

Expt. no.	Hours
1–2	6–7
3–4	10–11
5	13
6–7	16–17

There was a rapid initial improvement, but then again a decrease in concentration power in connection with a relapse as evidenced by massive pyuria and increased sedimentation rate. *Co* = E. coli; *Ent* = Enterococci.

Discussion

The capacity of the kidneys to produce a concentrated urine has been investigated in 6 infants during the weeks following an acute urinary tract infection. In 5 cases the urinary solute concentrations were low during the first weeks after infection and subsequently returned to normal in a systematic fashion. This suggests that acute urinary tract infections often cause a temporary reduction of the renal concentration capacity. Since the studies concern infants, some physiological maturation of renal function during the time of observation, could possibly have contributed to the increase in urinary solute concentration observed. However, to judge from studies which are in progress in infants without kidney disease, it seems improbable that this influence was of any significance, at least during the phase of rapid increase in urinary solute concentration.

The functional incapacity does not appear to be due to osmotic diuresis caused by loss of nephrons (Platt, 1952), as the dilution capacity was retained in all cases. Intracellular potassium deficiency has been described by Schwartz & Relman (1953) to cause a renal concentration incapacity. Since there were no other clinical signs of potassium depletion in the present cases it seems improbable that this mechanism was the cause of the reduced concentration ability.

It seems more probable to assume a structural damage to the part of the nephron responsible for renal water economy, namely the distal tubules and the collecting ducts, cf. Smith (1952) and Wirz (1957). From the conclusions of these authors it appears that normally in antidiuresis an isotonic urine enters the collecting ducts where hypertonicity is achieved. In the cases presented here the finding during antidiuretic conditions of a urine concentration close to a supposed plasma concentration of 280–300 mOsm/l. would then suggest a damage to the collecting ducts. However, such a finding also could occur as a consequence of isolated distal tubular damage or a combination of collecting duct and distal tubular damage.

Investigations performed by Weyrauch & Rosenberg (1954) speak in favour of the supposition that the decreased concentration capacity is caused by damage to the collecting ducts. They found that in experimental pyelonephritis, urogenous as well as hematogenous, the infection seemed to spread from the cortico-medullary junction of the kidney to the collecting ducts. This part of the nephron is also often found to be the seat of necrosis, inflammatory changes and dilatation in acute pyelonephritis, Craig (1935), Staemmler (1957).

The changes in renal function demonstrated here confirm, from the functional point of view, the fact most definitely settled by Chown (1947), Wilson & Schloss (1929), Craig (1935) and Weiss & Parker (1939) in their

histological studies that the acute, febrile urinary tract infection, the so-called cysto-pyelitis, often is a disease affecting the renal parenchyma.

The demonstration in the present cases of a decrease in the renal concentration ability shows that even in acute pyelonephritis there might be changes in renal function similar to those earlier demonstrated to exist in chronic pyelonephritis (Longcope & Winkenwerder (1933), Brod (1956)). These authors showed that the typical renal function pattern in chronic pyelonephritis was characterized by a marked decrease in concentration capacity in the presence of normal dilution ability.

In spite of the decreased water conservation capacity there were no or only slight clinical signs of dehydration in the form of decreased skin elasticity in the cases described, which is in marked contrast to the severe dehydration often seen in cases complicated by low urinary tract obstruction with hydronephrosis (Ericsson, Winberg & Zetterström (1955)). This discrepancy might be explained by the fact that in some of the latter cases there is an abnormal loss of water and cations (Zetterström, Ericsson & Winberg (1958)), while in the former there is an increased loss of water, but a normal conservation of cations, as evidenced by an intact renal acidification mechanism. As a matter of fact Marriott (1947) has pointed out that the dehydration reaction is due to a shrinkage of the extracellular space, and hence loss of sodium while pure water deficit results in thirst, but not, unless very grave, in subcutaneous desiccation, decreased skin elasticity and so forth. Laron (1957) has arrived at the same conclusions. Thirst is a symptom hard to evaluate in infancy. However, it probably was present in Case 6.

The clinical implications of the present study can be summarized as follows. Even in the fairly mild, acute urinary tract infections of infancy, usually classified as cysto-pyelitis, the infection may often be localized to the renal parenchyma, causing a reduction in renal function. Most recently this has been stressed by Linneweh (1957) who demonstrated a delayed excretion of phenol red in this disease. Normal urinary sediment and normal sedimentation rate do not exclude persisting renal damage.

The renal damage is easily overlooked since clinical symptoms of dehydration are usually missing, as a consequence of the fact that the damage may produce a water deficit but not salt depletion. However, thirst may be a feature in the disease.

From therapeutic point of view the demonstration of parenchymal involvement gives further emphasis to the opinion that in treating these infections it is not enough to sterilize urine, it is necessary to use chemotherapeutic doses sufficient to give adequate concentrations within the renal parenchyma to prevent tissue destruction.

Summary

Six infants with acute, febrile, non-obstructive urinary tract infection have been examined with respect to the renal concentration capacity. This was found to be lowered in 5 of these 6 cases. The findings suggest a damage most probably localized to the collecting ducts and it is concluded that such impairment is often present even in the mild cases of urinary tract infections in infancy, often classified as cysto-pyelitis. The implications of these findings are briefly discussed.

Concentration de la capacité rénale pendant les infections aiguës du tractus urinaire, non-obstructif, chez les nourrissons et les jeunes enfants.

Six enfants avec une infection aiguë febrile du tractus urinaire non-obstructif ont été examinés pour la capacité de la concentration rénale. Dans 5 sur ces 6 cas, on a trouvé celle-ci diminuée.

Les résultats suggèrent une détérioration assez étendue dans les canaux collecteurs et on conclut qu'une telle diminution est souvent trouvée même dans les cas d'infection faible du tractus urinaire chez les nourrissons, souvent classés comme cystopyélite. Les conséquences de ces résultats sont brièvement discutées.

Konzentrationskapazität der Nieren während akuter, nicht obstruktiver Harnweg-Infektionen bei Säuglingen und in der frühen Kindheit (Kleinkindern).

Sechs Kinder mit akuter, nicht obstruktiver, Harnweg-Infektion wurden im Hinblick auf Nierenkonzentrationsfähigkeit untersucht. Diese war in 5 von 6 Fällen auffallend vermindert. Die Untersuchungen weisen auf einen ziemlich ausgedehnten Schaden an den Sammelkanälchen und man folgert daraus, dass diese Beeinträchtigung oft gerade in milden Fällen von Harnweginfektionen vorkommt und öfters als Cystopyelitis klassifiert wird. Die Ergebnisse dieser Untersuchungen werden kurz diskutiert.

Capacidad de concentración renal en las infecciones agudas, no obstructivas, de las vias urinarias en la infancia.

Se exploró la capacidad de concentración renal en 6 niños con infección aguda febril, no obstructiva, de las vias urinarias. En 5 de estos 6 casos se halló muy disminuida. Ello sugiere la existencia de extensas lesiones de los túbulos colectores, concluyéndose en que estas alteraciones se presentan a menudo incluso en las infecciones moderadas de las vias urinarias, en la infancia, clasificadas con frecuencia de cistopielitis. Se discuten brevemente las deducciones a que llevan las anteriores observaciones.

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Vitamin B_{12} and Retinopathy in Juvenile Diabetics

by TORE KORNERUP and LARS STRÖM

It has been suggested that the adrenal cortex plays a part in the pathogenesis of diabetic vascular degeneration; to test this hypothesis a number of clinical observations have been carried out; except for the established fact that adrenalectomy does not arrest the progress of proliferative diabetic retinopathy (4) no other definite findings can at the moment be recorded. Until more experimental data are available the influence, if any, of the adrenal corticoid hormone upon diabetic vascular disease must remain purely hypothetical.

Some workers have postulated an antagonistic action between corticoid hormones and vitamin B_{12} (8, 9) also present in diabetes (1, 2, 7). The actual significance of this in diabetic vascular degeneration is obscure. The vascular damage in diabetes is partly due to a deposit in the vascular wall of polysaccharides and lipoids. The serum lipoproteins in diabetes differ from those in non-diabetics. On account of its lipotropic action B_{12} may play some part in the lipoid metabolism.

Some workers did not observe any clinical improvement of the diabetic retinopathy after giving vitamin B_{12} alone (3, 10) or in conjunction with testosterone (3). On the other hand Lederer *et al.* (6) have reported decreased capillary fragility in diabetics with retinopathy after treatment with B_{12} and in some cases an improvement of the retinopathy was observed.

Diabetic vascular degeneration is clinically and socially a grave problem; for this reason any treatment theoretically sound must be given a fair trial.

The result of giving a group of young diabetics B_{12} for a period of two years is now given.

Own Investigations

B_{12} was given subcutaneously to a group of 15 juvenile diabetics, i.e. diabetics whose disease started before 15 years of age. Twenty-two juvenile diabetics who had received no B_{12} treatment were used as controls. Apart

TABLE 1

Distribution of cases according to duration of diabetes when B_{12} treatment was started.

Duration	B_{12}-treated cases	Controls	Σ
0–4	—	1	1
5–9	4	18	22
10–14	8	3	11
15–	3	0	3
All durations	15	22	37

from the B_{12} administration both groups had identical treatment with adequate insulin and some restrictions as regards milk, bread and potatoes. No sweets were allowed.

The distribution of the cases according to duration of diabetes and age of patient at onset of diabetes is seen from Tables 1 and 2.

B_{12} was administered subcutaneously in an average dosage of 100 γ/day together with the insulin. The treatment was continued for two years. The patients were examined at least twice a year. Direct and indirect ophthalmoscopy was carried out. Retinopathy was said to be present when even single haemorrhages, aneurysms or dots of "exudate" were seen. In those cases where no aneurysms were seen the examination was repeated in monochromatic green light. When even this method of examination failed to reveal any microaneurysms or venular irregularities the case was considered to be free from retinopathy. To facilitate a comparison at a later examination colour photographs were taken of the fundus.

The result of the fundus examination carried out one and two years after B_{12} treatment was started is seen in Table 3. It should be noted, that retinopathy especially in its early phases has a fluctuating course which is illustrated by the appearance and disappearance of haemorrhages and exudates.

TABLE 2

Distribution of cases according to age at onset of diabetes.

Age at onset	B_{12}-treated cases	Controls	Σ
0–4	6	9	15
5–9	9	7	16
10–14	0	6	6
All ages	15	22	37

TABLE 3

	No. of B_{12}-treated cases		No. of controls	
	With retinopathy	Without retinopathy	With retinopathy	Without retinopathy
At onset of B_{12} treatment	15	0	8	14
Av. duration of diabetes (yrs)	11.8	—	8.5	7.6
One year after onset of B_{12}	8[a]	7	7	15
Av. duration	13.9	11.7	9.7	8.5
Two years after onset of B_{12}	7	8	10	12
Av. duration	14.2	13.6	10.3	9.6

[a] Two of these were markedly improved.

The treatment with vitamin B_{12} was started on 15 patients with an average duration of diabetes of 11.8 years. The cases belonging to this group are selected as 100% had retinopathy; according to Kornerup (5) the frequency of diabetic retinopathy in patients with this duration is about 75%.

The average duration of diabetes in the control group is 7.9 years. As regards frequency of retinopathy this group is selected as the actual frequency of retinopathy is 36% whereas it is expected to be about 50%.

Thus, when the investigation started, the group to be treated with B_{12} was on the whole in a worse condition than the control group. The longer average duration of diabetes in the B_{12} group means that, according to Kornerup (5), the intensity of one manifestation of diabetic vascular disease namely retinopathy is at least 1.5 times as high as that of the control group. In this special investigation the intensity is in reality higher as the frequency of retinopathy is 100%.

After one year of B_{12} treatment seven of the treated patients did not show any signs of retinopathy. The average duration of diabetes was now 12.8 years. Of diabetics within this duration group 80% have retinopathy (5) whereas in the actual group 53% have retinopathy. Thus, after one year's treatment the frequency of retinopathy had fallen from a value far above the expected average to a value far below. In the control group the proportion of cases with retinopathy had not changed during the past year as 32% were found to have retinopathy.

After two years treatment the number of cases without retinopathy was eight. The average duration of the treated group was now 13.6 years and whereas 80% were expected to have retinopathy (5) only 47% had this complication. In the control group the proportion of cases with retinopathy was 45%.

The group treated with B_{12} differs from the control group as the frequency of retinopathy decreases with duration contrary to other diabetics represented inter alia by the control group. In the control group having a better vascular condition from the start the frequency of diabetic retinopathy shows the well-known increase with duration.

Apart from an increased subjective feeling of well-being the B_{12} treatment was not found to have any other objective clinical effect. Neither the insulin requirement nor the relative blood pressure differed in either group.

In a case with advanced necrobioses one might have expected an amelioration or at least an arrest of the development of the cutaneous lesions during B_{12} treatment but no such effect was observed.

In a group of 22 adult diabetics B_{12} treatment has only in one case been followed by objective improvement in the state of the diabetic retinopathy.

No explanation can as yet be given for the mode of action of B_{12} in the cases mentioned above.

Of the 22 adult diabetics 16 had an age at onset before 15 years of age (2–14 years). The age of the patients when B_{12} treatment was started was 19–40 years (mean 27.4 years). The duration of diabetes at this moment was 15–28 years in 15 cases (mean 19 years) and nine years in one case.

This case, a girl of 19, showed a mild bilateral haemorrhagic retinopathy when B_{12} treatment started in 1954. After three years' treatment no haemorrhages or aneurysms could be detected.

In all the other cases having a considerably longer duration of diabetes when the B_{12} treatment started the retinopathy was uninfluenced or even deteriorated. A proliferative retinopathy was present in eight cases and all had a disastrous course.

It is noteworthy that a curative effect of B_{12} was seen only in incipient haemorrhagic retinopathy in young diabetics whose disease started before 15 years of age.

Summary

In order to study the therapeutic effect of vitamin B_{12} on the retinopathy in juvenile diabetics a daily dosage of 100 γ was given to a group of 15 cases of diabetes with an age at onset less than 15 years. A group of 22 juvenile diabetics having the same dosage of insuline but no B_{12} were controls. All cases were examined repeatedly during two years.

In the treated group the frequency of retinopathy decreased during the time of observation whereas in the control group the frequency showed the usual increase with duration.

It seems as if treatment with vitamin B_{12} were of some significance in delaying the development of incipient retinopathy in juvenile diabetics.

Effets de la Vitamine B_{12} sur la rétinopathie chez les jeunes diabétiques.

En vue d'étudier l'activité thérapeutique de la vitamine B_{12} sur la rétinopathie chez les jeunes diabétiques, les auteurs ont administré une dose de 100 gammas par jour à un groupe de quinze sujets diabétiques dont la maladie s'était déclarée au plus tard à l'âge de quinze ans Les sujets témoins furent fournis par un autre groupe de 22 autres jeunes diabétiques qui reçurent les mêmes doses d'insuline mais sans adjonction de vitamine B_{12}. Tous ces malades furent examinés à des intervalles réguliers durant deux ans. Pendant cette période d'observation, la fréquence des rétinopathies diminua chez les patients auxquels on avait administré de la vitamine B_{12}, tandis que chez les sujets témoins, l'incidence de cette complication augmenta dans les mêmes proportions que d'habitude avec le temps. Il semble donc que l'administration de vitamine B_{12} ait eu une certaine influence pour retarder l'apparition des débuts de rétinopathies chez les jeunes diabétiques.

Vitamin B_{12} und Retinopathie bei jugendlichen Diabetikern.

Um den therapeutischen Effekt von Vitamin B_{12} auf die Retinitis bei jugendlichen Diabetikern zu studieren, wurde eine tägliche Dosis von 100 gamma einer Gruppe von 15 Fällen mit Diabetes, bei denen die Krankheit im Alter von weniger als 15 Jahren zuerst aufgetreten war, verabreicht. Eine Gruppe von 22 Diabetikern, die dieselbe Insulindosierung aber kein Vitamin B_{12} erhielt, diente als Vergleich. Alle Fälle wurden durch zwei Jahre wiederholt untersucht. Bei der mit Vitamin B_{12} behandelten Gruppe nahm die Häufigkeit der Retinopathie während der Beobachtungszeit ab, während bei der Vergleichsgruppe die Inzidenz den gewöhnlichen mit der Dauer des Krankheitsprozesses einhergehenden Anstieg aufwies. Es scheint, dass die Behandlung mit Vitamin B_{12} eine gewisse Bedeutung für den Aufschub in der Entstehung der Retinopathie bei jungen Diabetikern haben könnte.

Vitamina B_{12} y retinopatía en diabéticos juveniles.

A fin de estudiar la acción terapéutica de la vitamina B_{12} sobre la retinopatía en la diabetes juvenil se administró una dosis diaria de 100 gammas a un grupo de quince casos de diabetes con una edad de comienzo, inferior a los quince años. Se utilizó como control un grupo de 22 diabéticos jóvenes tratados con la misma dosis de insulina pero sin vitamina B_{12}. Todos los casos fueron explorados repetidas veces durante dos años. En el grupo sometido a tratamiento, la frecuencia de la retinopatía disminuyó mientras que en el grupo control la frecuencia presentó el habitual incremento. Parece como si el tratamiento con vitamina B_{12} tuviera cierta significación en demorar el desarrollo de la retinopatía incipiente en la diabetes juvenil.

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Haemoglobin H and Inclusion-Body Anaemia in a Swedish Family

by F. HEDENBERG, U. MÜLLER-EBERHARD, S. SJÖLIN and L. WRANNE

Since Rigas, Koler & Osgood (1955), and Gouttas, Fessas, Tsevrenis & Xefteri (1955) independently reported the first cases of an anaemia associated with haemoglobin H and coccoid inclusion bodies in the red cells several new cases have been presented (Motulsky, 1956; Lehmann & Singh, 1956; Eng, Hin, Keng & Endenburg, 1957; Brain & Vella, 1958; Minnich, Na-Nakorn, Tuchinda, Pravit & Moore, 1958; and Wolff, Michaels & von Hofe, 1958). The cases hitherto described have been of Chinese, Greek, Philippine, Thai, Indonesian, Algerian, Arab, Malay, and Italian parentage.

The present paper is the first Swedish report. The case histories of two brothers suffering from anaemia of this type are described, and a haematological and genetic study of the family is also presented.

Methods

Routine haematological investigations were carried out by standard methods.

The haemoglobin was analysed by zone electrophoresis, employing potato starch as supporting medium as described by Kunkel, Ceppellini, Müller-Eberhard & Wolf (1957).

The concentration of alkali-resistant haemoglobin was determined by the method of Singer, Chernoff & Singer (1951). Our normal finding in adults is 0.40 % ± 0.22 (mean ± 2 SD).

Erythrocyte inclusion bodies were counted after supravital staining with 1% brilliant cresyl blue. To 0.05 ml of whole blood 0.05 ml of the dye was added. A smear was made after incubation of this mixture for one hour at a temperature of 37° C.

Sickle cell preparations were made with a 2% sodium metabisulphite solution as described by Daland & Castle (1948), and readings were made after 30 minutes, and in Case 1 and 2 every four hours for 24 hours.

The iron metabolism was studied by methods described by Garby, Sjölin & Vahlquist (1957).

The content of free porphyrins in the red cells was determined by the method of Schwartz & Wikhoff (1952), as modified by one of us (L. W.).

The red cell survival and the blood volume were measured with Cr^{51} tagged red cells in accordance with the principle of Gray & Sterling (1950). The normal apparant half life is 22–34 days (= ± 2 SD), by the method used in our laboratory.

The osmotic resistance of the red cells was determined by Ponder's method, as modified by Sjölin (1954).

The haptoglobin concentration was determined by the method of Laurell & Nyman (1957).

Case Reports

Case 1.—P. G. E., born March 20th, 1955. Anaemia was diagnosed for the first time at the age of 15 months. At the age of two years the boy was admitted to the Children's Hospital in Hälsingborg, when he was found to be rather pale, with anaemia and a low colour index. His general condition was good and his development normal. There was no history of any serious illness, and the diet did not seem to have been deficient in any respect. Treatment with iron, both orally and intramuscularly, was without effect, as was oral administration of liver preparations. Ever since the anaemia has been stationary with a haemoglobin concentration of 8–10 g/100 ml and a mean corpuscular haemoglobin of 21–24 $\mu\mu g$.

At the age of 3 years the boy was admitted to the Paediatric Department of the University Hospital in Uppsala, where he remained from April 9th to June 5th, 1958.

Clinical examination revealed nothing abnormal except for slight pallor. The tongue, hair, and finger nails were normal. There was no enlargement of liver, spleen, or lymphatic nodes. His physical and mental development seemed normal.

Laboratory investigations

Peripheral blood. The leucocyte and platelet counts were normal. The differential leucocyte count showed no abnormalities. The coagulation time, bleeding time, and prothrombin time were normal. The main data concerning the erythrocytes are listed in the Table. Blood films showed anisocytosis, poikilocytosis, polychromasia, and many target cells (Fig. 1). The red-cell-diameter distribution curve showed an increased number of large cells (Fig. 2). The reticulocyte count was moderately raised, and in several erythrocytes, coccoid inclusion bodies were found. After incubation with brilliant cresyl blue for one hour, numerous inclusion bodies appeared in 24% of the erythrocytes (Fig. 3). Sickle cell tests were negative.

Bone marrow. The cell count was normal. Myelopoiesis appeared to be normal. Erythropoiesis was brisk, with an increased number of polychromatic and oxyphilic cells. No signs of megaloblastic degeneration were found and the number of sideroblasts was not raised.

Total blood volume was 1230 ml (79 ml/kg) and the red blood cell volume 36[illegible] ml (23.4 ml/kg).

TABLE

Haematological data of Cases 1 and 2, and of four of their relations.

	Case 1 P.G.E.	Case 2 A.E.	Mother K.E.	Maternal aunt E.E.	Maternal grand-mother O.S.	Father G.E.
Haemoglobin g/100 ml	9.4–10.5	9.9	11.8	11.6	12.4	15.5
Red cell mill/cu.mm	3.8– 5.0	5.0	4.6	4.8	4.7	5.0
Haematocrit %	30–33	35	36	36	38	43
M.C.H.C. %	31–32	28	33	32	32	36
M.C.H. $\mu\mu$g	21–24	20	26	24	26	31
M.C.V. cu. μ	64–84	70	78	74	80	86
M.C.D. μ	8.0– 8.1	8.0	7.8	7.9	7.9	7.8
M.C.T. μ	1.5	1.4	1.3	1.5	1.6	1.8
Reticulocytes %	2.4– 4.7	1.6	1.0	0.6	0.7	0.4
Target cells %	10.4	8.5	a few	a few	a few	0
Red cells with coccoid inclusion bodies %	24	27	a few	a few	a few	very few
Hb–H % of total Hb	13.5	7.0	0	0	0	0
Hb–A_2 % of total Hb	1.3	1.2	2.1	2.5	3.0	2.5
Hb–F % of total Hb	0.8	1.0	0	0.7	0.5	0
Serum iron μg/100 ml	143	115	91	—	—	145
T I B C μg/100 ml	524	356	518	—	—	494
Free red-cell protoporphyrin $\mu\mu$g/100 ml	21; 27	140	17	—	—	22
coproporphyrin $\mu\mu$g/100 ml	0.5; 1.8	1.9	0.5	—	—	1.1

Tests for haemolysis and life span of the erythrocytes. The osmotic resistance of the red cells was increased (Fig. 4). The mechanical resistance was normal. Direct and indirect Coombs's tests were negative. The survival of the patient's Cr^{51}-tagged erythrocytes after autotransfusion was normal (apparent half life 23 days). The total serum bilirubin was 0.2–0.4 mg%. Three 24 hour samples of faeces contained 17 mg of urobilin per day, and three 24 hour samples of urine 0.2 mg of urobilin per day. The haptoglobin concentration was normal, at 70 mg/100 ml.

Characteristics of the haemoglobin.[1] On starch electrophoresis at pH 8.6 and ionic strength 0.05 an abnormal haemoglobin pattern was observed. Besides the normal components, there was a conspicuous amount (13.5%) of a haemoglobin which migrated in front of haemoglobin A, with an approximate rate of 4.5 electrophoretic mobility units (Fig. 5). The abnormal

[1] For the electrophoretic investigations we are greatly indebted to Dr. H. J. Müller-Eberhard.

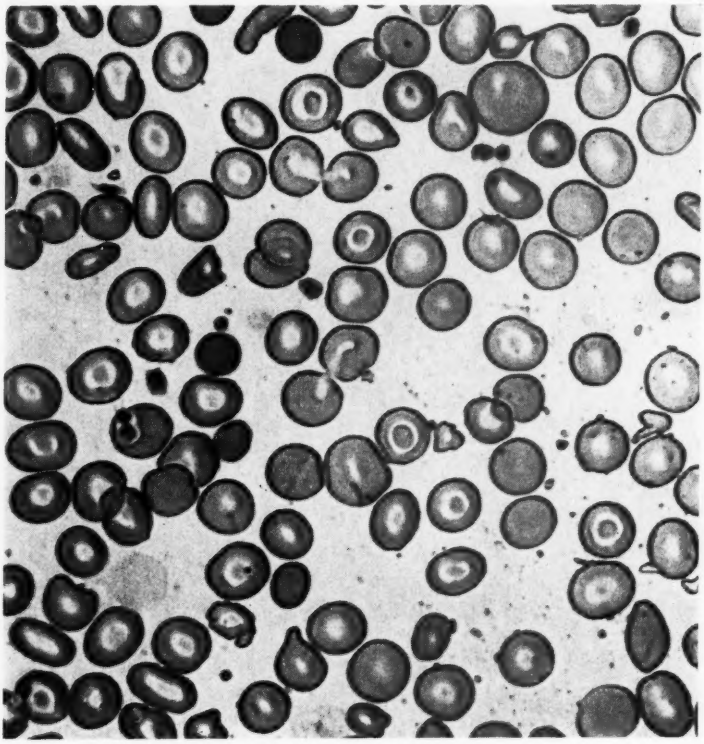

Fig. 1. Photomicrograph of a blood smear from Case 1.

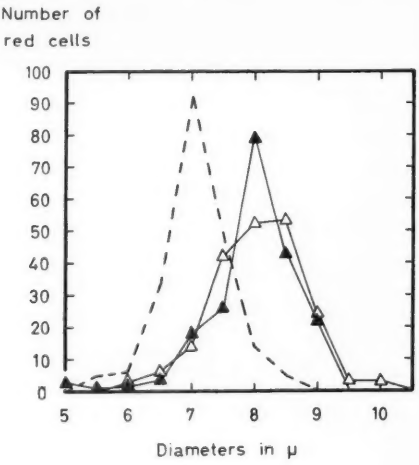

Fig. 2. Red-cell-diameter distribution curves of Cases 1 (△——△) and 2 (▲——▲). The dotted line indicates the mean normal curve.

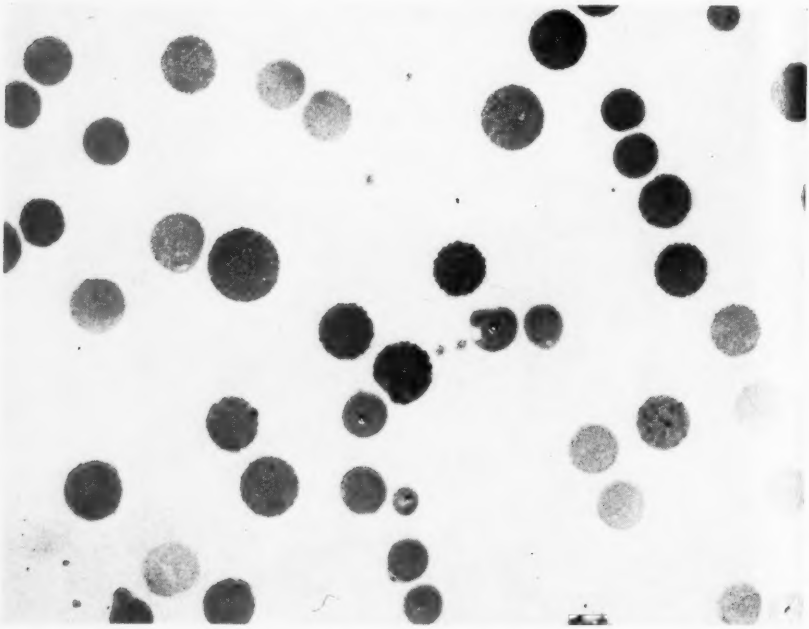

Fig. 3. Photomicrograph of a blood smear from Case 1, supravital staining with brilliant cresyl blue.

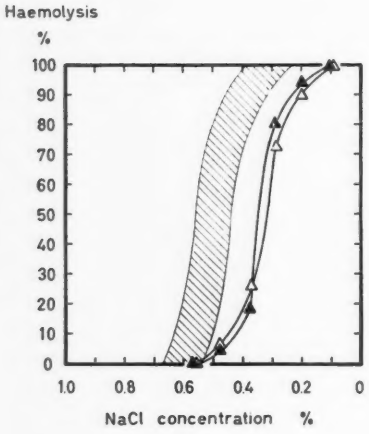

Fig. 4. Osmotic resistance curves of Case 1 (△——△) and 2 (▲——▲). The hatched area represents the normal variation (±2 SD).

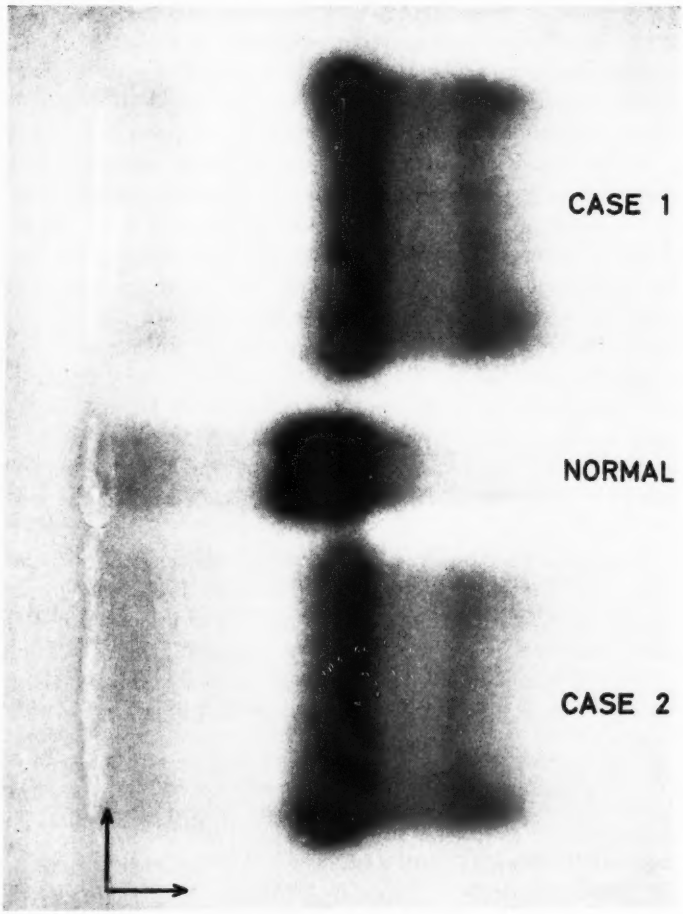

Fig. 5. Haemoglobin patterns of Cases 1 and 2, obtained by starch electrophoresis.

haemoglobin was irreversibly precipitable with brilliant cresyl blue. The solubility of the abnormal haemoglobin at neutral pH was low, as indicated by the appearance of a precipitate both when the solution was stored at room temperature and at + 4°C. With respect to mobility and solubility, the abnormal haemoglobin resembled haemoglobin H. Haemoglobin A_2, although clearly demonstrated in all experiments, was found to be present in only half the normal concentration. The material migrating between haemoglobin A and the abnormal component was interpreted as representing

haemoglobin A_3. This haemoglobin retained its intermediate electrophoretic mobility after isolation. Although no reliable data could be obtained, its concentration appeared to be higher than in normal haemolysates even if prepared from freshly drawn blood samples.

The concentration of haemoglobin F was not increased.

Iron metabolism. The serum iron, iron binding capacity, and mean corpuscular haemoglobin concentration were normal. (Table). The transcapillary exchange of Fe^{59} from plasma was slightly increased, the half time being about 53 minutes. The rate of incorporation of Fe^{59} into the circulating red cells was normal, but the total amount of iron incorporated was lower than normal, at about 45%. The serum copper was normal.

Porphyrin studies. The concentrations of free porphyrins in the red cells may be found in the Table. Compared with that of normal children of the same age, the protoporphyrin content was normal, though close to the lower limit, and the coproporphyrin was normal. The uroporphyrin was not determined. Urinary excretion of coproporphyrin, porphobilinogen, and δ-aminolaevulic acid were within the normal limits. No urinary uroporphyrin could be detected.

Other investigations. The erythrocyte sedimentation rate was low, and never exceeded 4 mm per hour. Liver function tests were normal. The gastric juice contained free hydrochloric acid after injection of histamine. The serum vitamin B_{12} concentration was 480 μμg/ml. The faeces contained no occult blood. Urinary analysis revealed no protein or sugar, and the sediment was normal. An X-ray of the skull was normal.

CASE 2.—A. E., born August 7th, 1957, was the only brother of Case 1. The boy had always seemed healthy. Routine examination at the age of 2 months had revealed nothing abnormal, and his haemoglobin concentration at that time was 11.0 g/100 ml. Because of his brother's illness the boy was examined at the Paediatric Department of the University Hospital, Uppsala, at the ages of 8 and 10 months.

Clinical examination in Uppsala was negative on both occasions. The main haematological data of the patient are listed in the Table. The findings in this case are very similar to those of Case 1, and the anaemia was characterized by a low mean corpuscular haemoglobin content and a low mean cell volume. The blood smears showed anisocytosis, poikilocytosis, and target cells. The red-cell-diameter distribution curve showed an increased number of large red cells (Fig. 2). After incubation with brilliant cresyl blue, numerous coccoid inclusion bodies appeared in 27% of the erythrocytes. Sickle cell tests were negative. The osmotic resistance of the red cells was increased (Fig. 4). Starch electrophoresis of the haemoglobin showed the same pattern as was found in Case 1 (Fig. 5). The haemoglobin H conce-

tration was 7.0%. The concentration of haemoglobin A_2 was about half the normal value, and the concentration of haemoglobin F was not increased. The serum iron, total iron binding capacity and mean corpuscular haemoglobin concentration were normal. Analysis of free red cell porphyrins showed a high but normal protoporphyrin level and a normal coproporphyrin content. Between the ages of 8 and 10 months the boy was treated with an oral iron preparation without any improvement in the anaemia.

Study of the Family

The pedigree of the two boys has been traced back to the great grandparents, and no consanguinity has been found (Fig. 6). The family was not aware of any ancestors from abroad.

In a haematological study of the family ten members from three generations have so far been investigated (Fig. 6). In nine of them the following laboratory procedures have been carried out. Haemoglobin concentration, red cell count, haematocrit reading, blood smear, brilliant cresyl blue staining for reticulocytes and inclusion bodies, Price-Jones curve, osmotic resistance of the red cells, sickle cell test, starch electrophoresis of the haemoglobin, and in some cases also serum iron, total iron-binding capacity and free red-cell porphyrins. In the tenth subject (a cousin) the haemoglobin concentration, red-cell count, blood smear, and brilliant cresyl blue staining for reticulocytes and inclusion bodies were assessed.

The mother (K. E.), one of her sisters (E. E.), and the maternal grandmother (O. S.) had no clinical signs and no anaemia, but showed definite haematological abnormalities (Table). Anisocytosis, poikilocytosis, and a few target cells were present in all of them, the red-cell-diameter distribution curves showed a slightly increased number of large red cells, the osmotic resistance of the red cells was increased (Fig. 7), after incubation with brilliant cresyl blue some of the erythrocytes showed numerous typical coccoid inclusion bodies. Tests for sickle cells were negative. In no case could an abnormal haemoglobin be demonstrated. The concentration of haemoglobin A_2 was found to be normal.

The father (G. E.) had no clinical signs, but had noticed repeated episodes of slight yellowing of the sclerae. His blood picture showed some abnormalities. There was anisocytosis, the red-cell-diameter distribution curve showed a slightly increased number of large red cells, and in two slides made on different occasions coccoid inclusion bodies were found in a very few red cells. In several other slides, as in many smears from normal newborns and adults, we were unable to find typical inclusions bodies. No target

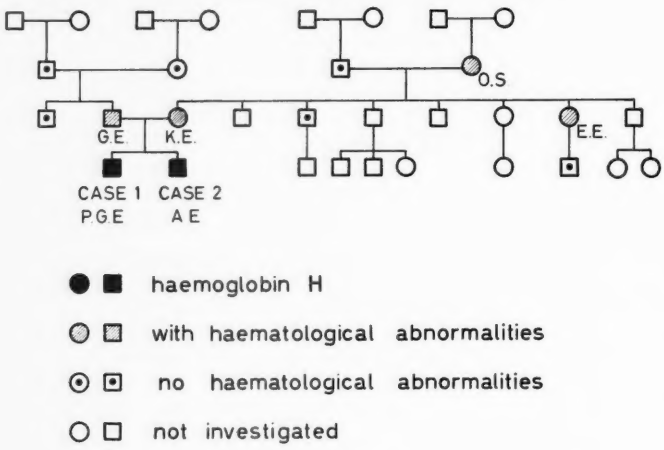

Fig. 6. Family tree.

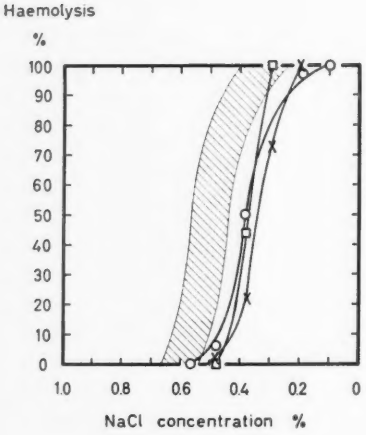

Fig. 7. Osmotic resistance curves of three relations (K. E. ○——○, E. E. ×——×, and O. S. □——□). The hatched area represents the normal variation (±2 SD).

cells were seen, and the osmotic resistance of the red cells fell within the normal limits. No abnormal haemoglobin could be demonstrated, and the concentration of haemoglobin A_2 was normal.

The other six relations investigated showed no abnormalities.

Discussion

In the two brothers described the main haematological findings were moderate, microcytic anaemia, target cells, erythrocyte coccoid inclusion

bodies, and 7 and 13.5% haemoglobin H. A congenital anaemia of this type is known as haemoglobin H disease or trait, or haemoglobin H—thalassaemia disease. Most of the carefully investigated cases in the literature also showed clinical signs of hyperhaemolysis. In three patients, in whom red cell survival was studied, the life span of the red cells was abnormally short (Rigas, Koler & Osgood, 1956; Motulsky et al., 1958). In our two cases definite signs of hyperhaemolysis were lacking, and in Case 1 red-cell survival was shown to be normal. Thus it seems likely that haemoglobin H anaemia need not necessarily be haemolytic in character.

In an attempt further to investigate the nature of the anaemia the iron metabolism was studied. In both cases the serum iron and the total iron-binding capacity were found to be normal. These findings are inconsistent with iron deficiency. In Case 1 the iron metabolism was also studied by means of Fe^{59} intravenously injected. The rate of transcapillary exchange of iron was demonstrated to be moderately increased. The rate of incorporation of Fe^{59} into the red cells was normal, but the total percentage of Fe^{59} incorporated after two weeks was considerably below the normal value. These findings are at present difficult to interprete. If the rate of disappearance of plasma iron does indeed reflect the erythropoietic activity, the latter ought to be increased in this case. This is corroborated by the moderately increased number of reticulocytes and the erythroid hyperplasia of the bone marrow. The small fraction of Fe^{59} incorporated into the peripheral red cells indicates that a large part of the tagged iron is continually lost (? in the marrow) and slowly re-utilized. It seems thus possible that a number of the red cells formed have an extremely short survival time, and escape detection by the chromium method (cf. Garby, Sjölin & Vahlquist, 1957). This hypothetical interpretation, however, does not permit the unequivocal diagnosis of a haemolytic process, especially as the haptoglobin concentration, and urobilin excretion were normal.

The analysis of free red-cell porphyrins gave varying results in the two cases; but in no case were the findings definitely abnormal, and they do not help to explain the anaemia.

Thus the true nature of the anaemia remains obscure.

Certain laboratory findings in some of the relations of our two cases are of interest in the elucidation of the mode of inheritance of haemoglobin H.

It has been reported that some relations of patients suffering from haemoglobin H disease have shown microcytosis, anisocytosis, poikilocytosis, and target cells, with or without anaemia. Their red cells have often shown increased osmotic resistance, but neither erythrocyte inclusion bodies nor an abnormal haemoglobin have been found. These relations have all

been thought to have the thalassaemia trait. In cases in which one of the parents of the affected patient had haematological abnormalities of the type above described, the other parent appearing haematologically normal, the latter parent was suggested to be a heterozygous carrier of the haemoglobin H gene. Further, it has been suggested (Eng, Hin, Keng & Edenburg, 1957) that haemoglobin H is inherited in a manner similar to the other abnormal haemoglobins, but that the amount of haemoglogin H in the trait form is not sufficient to be demonstrable by electrophoresis unless its penetrancy is increased by the presence of another pathological gene such as that of thalassaemia. They concluded that the affected patients were heterozygous for the thalassaemia gene and heterozygous for the haemoglobin H gene, having received one of these genes from each of the parents.

Another pattern of inheritance was described by Minnich, NaNakorn, Tuchinda, Pravit & Moore (1958). In three of their families one of the parents was found to be haematologically normal and the other showed erythrocyte inclusion bodies. In one of the families erythrocyte inclusion bodies were found in three generations. In these families the inclusion body anaemia seemed to be related to thalassaemia trait, however. For example, signs of thalassaemia trait were found in siblings of patients with inclusion body anaemia.

Recently Kunkel, Ceppelini, Müller-Eberhard & Wolf (1957) have found that in 32 out of 34 cases of thalassaemia trait the normal minor haemoglobin A_2 was increased. In 23 parents of children with thalassaemia major investigated by Gerald & Diamond (1958) the haemoglobin A_2 concentration was raised. Josephson, Masri, Singer, Dworkin & Singer (1958) were able to confirm a raised haemoglobin A_2 concentration in 32 patients with thalassaemia trait so far studied. In relations of published cases suffering from haemoglobin H disease the amount of haemoglobin A_2 has not yet been estimated. In those relations of our patients, who presented a thalassaemia-like blood picture, a normal haemoglobin A_2 concentration was found. The presence of thalassaemia trait in these persons may therefore probably be excluded.

The presence of haemoglobin A_2 in half the normal concentration in our two patients is worthy of note. Wolff, Michaels & von Hofe (1958) reported haemoglobin A_2 to be virtually absent in the case they investigated. Riggs, Koler & Osgood (1956) mentioned the presence of haemoglobin A_2 in their three patients. These authors performed electrophoretic analysis in a Tiselius apparatus, but they did not publish any figures.

Gouttas, Fessas, Tsevrenis & Xefteri (1955) found that haemoglobin preparations obtained from blood with known haemoglobin H content did not show the haemoglobin H on electrophoresis if the erythrocytes had pre-

ously been stained with brilliant cresyl blue and then washed repeatedly with normal saline. They therefore suggested that coccoid inclusion body formation is related to the presence of the abnormal haemoglobin. Later several other authors have conducted similar experiments. Their findings and our own observations have confirmed that haemoglobin H is precipitated by brilliant cresyl blue.

In the mother of our patients a few red cells contained unmistakeable coccoid inclusion bodies. Coccoid inclusion bodies were also detected in exceedingly few red cells from the father. Having regard to the relationship between inclusion bodies and haemoglobin H, and to the absence of thalassaemia in the family, we are inclined to believe that both parents have the haemoglobin H trait, and that the two boys are homozygous for the haemoglobin H gene.

Acknowledgements

We wish to thank Professor B. Vahlquist and Associate Professor G. Wallenius for their help and interest. We acknowledge the invaluable technical assistance of Mr. S. Foconi.

Summary

The cases of two Swedish brothers with haemoglobin H and inclusion-body anaemia are reported. Investigation of the family tree revealed no consanguinity, but definite haematological abnormalities were found in several of the relations. No abnormal haemoglobin has been detected in nine relations so far investigated, however. It does not seem likely that any member of the family has thalassaemia trait, since all those investigated have had a normal haemoglobin A_2 concentration. The evidence of erythrocyte coccoid inclusion bodies in both parents, a feature which with all probability is closely related to the abnormal haemoglobin, suggests that both are heterozygous for the haemoglobin H gene, and that their two sons are homozygous for the same gene.

Hémoglobuline H et anémie d'inclusion dans une famille suédoise.

On rapporte les cas de deux frères suédois ayant une hémoglobine H et une anémie d'inclusion. Selon les investigations d'arbre généalogique, on n'a pas trouvé de consanguinité mais des anomalies hématologiques définies chez plusieurs membres de la famille. Cependant, aucune anomalie de l'hémoglobine n'a été constatée chez les neuf parents sous contrôle. Il ne semble pas probable qu'un des membres de cette famille souffre d'une thalassémie ou qu'il en soit prédisposé, étant donné que tous ceux examinés ont eu une concentration normale d'hémoglobine A_2. Le fait que les deux parents présentent des corps érythrocytes d'inclusion — une caractéristique qui très probablement est étroitement liée à une hémoglobine anormale — suggère que les deux parents sont hétérozygotes au gène de l'hémoglobine H, et que leur deux fils sont homozygotes au même gène.

Hämoglobin H und Einschlusskörperchen-Anämie in einer schwedischen Familie.

Es wird über das Vorkommen von Hämoglobin H und von erythrozytären Einschlusskörperchen bei zwei Brüdern einer schwedischen Familie berichtet. Durch Untersuchung der weiteren Familie wurde erwiesen, dass keine Blutverwandtschaft vorliegt. Eine eingehende klinische Untersuchung erbrachte, dass mehrere der Verwandten der beiden Brüder eindeutig abnormale hämatologische Befunde aufwiesen. Keiner der 9 Familienmitglieder, die neben den beiden Brüdern untersucht wurden, hatte das abnormale Hämoglobin. Da die Konzentration von Hämoglobin A_2 in allen untersuchten Fällen mit Ausnahme der beiden Patienten normal war, ist es unwahrscheinlich, dass Thalassämia minor in der Familie vorkommt, trotzdem die anderen hämatologischen Befunde daran denken liessen. Da bei beiden Eltern coccoide erythrozytäre Einschlusskörperchen gefunden wurden und da diese Einschlusskörperchen mit grosser Wahrscheinlichkeit an das Vorkommen von Hämoglobin H gebunden sind, erscheint es möglich, dass beide Eltern heterozygote Träger der Hämoglobin H Eigenschaft sind und dass die beiden Söhne die homozygote Anlage für das abnormale Hämoglobin besitzen.

Hemoglobina H y anemia de cuerpos de inclusión en una familia sueca.

Se describe el caso de dos hermanos suecos en cuyo cuadro hematológico se encuentran hemoglobina H y cuerpos de inclusión. La investigación del árbol familiar no relevó ninguna consanguinidad, pero se encontró que varios de los parientes de dichos hermanos presentaban abnormidades hematológicas. Ninguno de los nueve familiares que se examinaron, aparte de los dos hermanos, tenía la hemoglobina anormal. Como la concentración de hemoglobina A_2 en todos los casos investigados, con excepción de los dos pacientes, era normal, no es probable que la familia sufriese de talasemia menor, a pesar de que los demás hallazgos hematológicos podían dejarlo suponer. Habiéndose encontrado en ambos padres cuerpos de inclusión eritrocíticos y ya que dichos cuerpos de inclusión probablemente están fijados a la hemoglobina H, hay que suponer que ambos padres son portadores heterocigóticos de la hemoglobina H y que los dos hermanos tienen el factor hereditario homocigótico para la hemoglobina anormal.

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CASE REPORT

Generalized Herpes Simplex Infection Associated with Staphylococcal Septicemia in a Newborn Infant

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The rare instances of infection with herpes simplex virus reported in the newborn have a clinical course generally described as fulminant and causing death within a few days. This is considered in part to be due to the fact that the immature tissues of newborns are a suitable medium for rapid growth of the virus. In the cases reported previously, mostly virologic studies and no extensive bacteriologic examination were carried out.

The present report concerns a 15-day-old female with a fulminant clinical course in which staphylococcus septicemia coexisted with herpetic infection.

Case Report

Clinical course

An 8-day-old female infant was admitted to the Pediatric Clinic, Karolinska Sjukhuset, because of symptoms of neonatal septicemia. She was the product of an uneventful pregnancy. The mother was delivered in a hospital. Birth weight of the infant, 2650 g. The first week of life the course was unremarkable. On the 8th day the baby had a nasal discharge and fever. There was auscultatory and radiologic evidence of bilateral bronchopneumonia. Staphylococcus aureus was cultured from nasal and pharyngeal secretions and from cerebro-spinal fluid on the day prior to death. On tetracyclin treatment, the patient seemed to recover and she became afebrile on the 12th day. On the next day, however, she went rapidly down-hill and had profuse bleeding from puncture marks in the fingers. Rapid enlargment of the liver developed, the stools became pale and clay-coloured and despite chloramphenicol and sulfathiazole intravenously and blood transfusions the baby went into shock and expired on her 15th day of life after seven days of illness.

Pathology

The autopsy was performed 4 hours post mortem. The body was that of a fairly well nourished female infant weighing 2680 g and measuring 52 cm in length. The skin was pale and showed numerous ecchymoses around puncture marks in the legs, but no vesicles or pustules. There was no eczema.

On opening the body cavities the following pertinent findings were noted. The liver was enlarged, with a weight of 145 g (normal 123 g) and was reddish-brown displaying numerous yellowish-white dots measuring 1–2 mm in diameter. These round areas were equally distributed in the right and left lobes and subcapsularly as well as on the entire cut surface. The intervening parenchyma was congested and fragile. The lymphnodes of the porta hepatis were not enlarged.

The spleen was enlarged, weighing 24 g (normal 10 g). It was firm, dark red and congested. No areas of necrosis were seen.

The adrenals were of normal size and showed no obvious gross changes.

The mucosa of the tongue and pharynx and the upper two thirds of the esophagus were intact. The lower third of the esophagus showed ulcers of the mucosa. The stomach and intestines were normal.

The heart weighed 20 g and showed small areas of yellowish necrosis subendocardially on the right aspect of the interventricular septum. The remainder of the gross examination was negative. The lungs, kidneys and brain revealed no necroses, or other gross changes. The skeleton and striated muscles were normal.

Microscopic examination showed changes in the liver, spleen, adrenals, esophagus, heart, and brain with acellular necroses and intranuclear inclusion bodies.

The *liver* displayed wide-spread hemorrhagic necrosis and the major part of the liver cells showed various degree of disintegration. No accurate localization of the necrosis within lobules could be ascertained. Several liver cell nuclei showed vacuolar degeneration with peripheralization of the chromatin that was clumped together towards the nuclear membrane. In some of these cells intranuclear acidophilic inclusions were found. They were surrounded by a clear halo. The inclusions were of Cowdry type A. No infiltration of inflammatory cells were present, nor were any bacteria or fungi found in Gram- and PAS-stains.

The *spleen* was congested and contained numerous hemorrhagic necroses. Several reticuloendothelial cell nuclei showed vacuolar degeneration and a few of these displayed acidophilic inclusions, type A.

The *adrenals* contained several cone-shaped cortical necroses with the base of the cone towards the capsule. They were acidophilic and had the appearance of coagulation necroses. There were no inflammatory cells present. In a few capillaries small acidophilic, hyaline thrombi were present. No bacteria were found in Gram-stained sections. The fetal cortical cells surrounding the necrotic areas showed vacuolar degeneration of their nuclei. Several of these cells presented intranuclear, acidophilic inclusions surrounded by clear halos.

The *esophagus* near the junction with the stomach showed a localized ulceration with desquamated epithelium and granulation tissue containing collections of Gram-positive cocci on the surface and lodging in pockets of the submucosa. There were very few leukocytes and plasma cells and occasional lymphocytes. Areas of hyaline, acidophilic coagulation necrosis were found near the muscle layer. In these necrotic areas vacuolar degeneration of cell nuclei was present and in the submucosa adjacent to the necrotic part acidophilic intranuclear inclusion bodies were present in reticuloendothelial cells. Also, the esophageal epithelium adjacent to the ulceration contained intranuclear inclusions of type A.

The *heart* showed small subendocardial coagulation necroses with very occasional inclusion bodies in myocardial cells.

The *brain* contained no areas of wide-spread necrosis, but in the basal cortical layer of the frontal, parietal and occipital lobes intranuclear inclusions with poor haloing

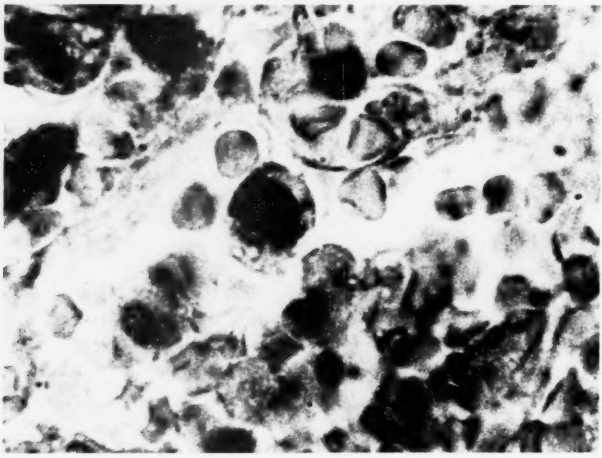

Fig. 1. *Liver.* In center, liver cell with nucleus showing slight vacuolization of center and early fragmentation of chromatin with peripheralization towards nuclear membrane. Hematoxylin–eosin. × 900.

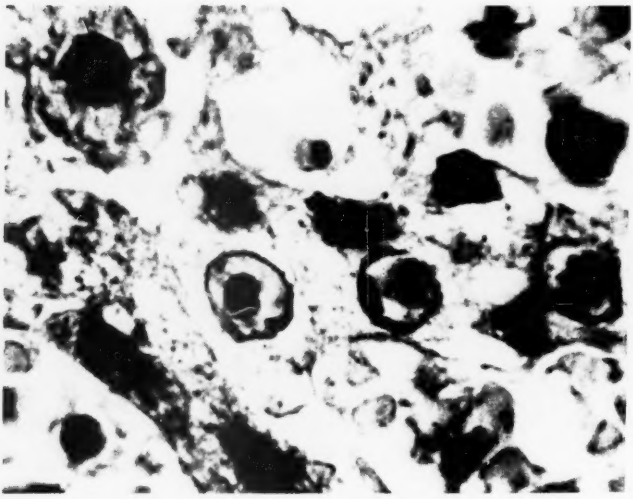

Fig. 2. *Liver.* Three liver cells with intranuclear inclusion bodies, type A. Note halo and peripheralization of chromatin. H & E. × 900.

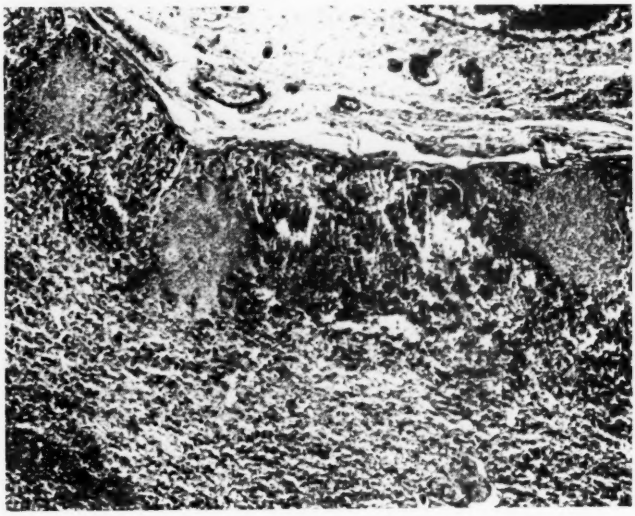

Fig. 3. *Adrenal.* Cortical areas of hyaline coagulation necrosis. H & E. ×70.

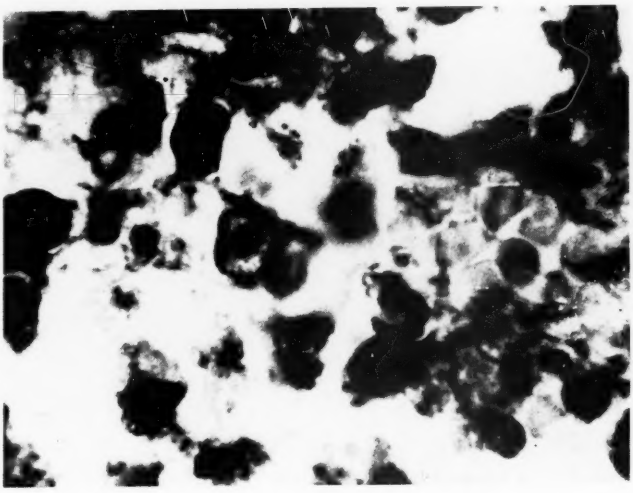

Fig. 4. *Adrenal.* Periphery of one of the necroses shown in Fig. 3. Note cell with intranuclear inclusion in center. H & E. ×900.

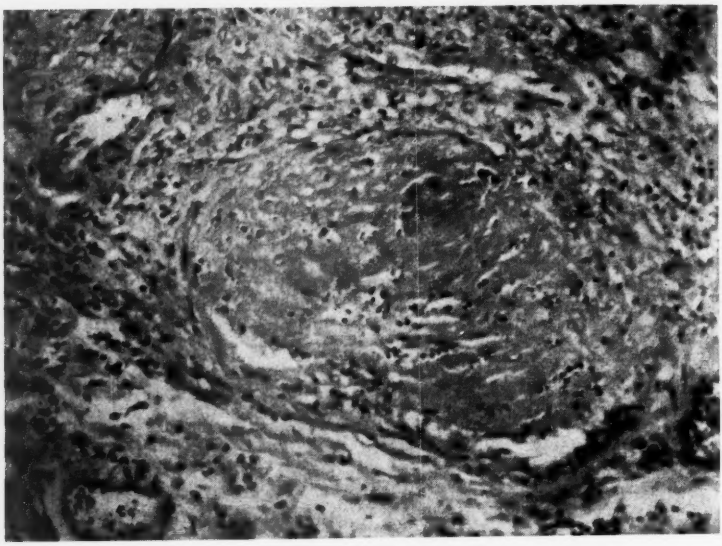

Fig. 5. *Esophagus.* Submucosa with area of acidophilic coagulation necrosis adjacent to muscle layer. H & E. ×100.

Fig. 6. *Esophagus.* Intranuclear inclusion body of cell adjacent to the area of necrosis shown in Fig. 5. H & E. ×1000.

were encountered. Similar changes were noted in astrocytes of the subcortical white matter. The cells of the pia mater showed vacuolar nuclear degeneration but no inclusions were found.

No inflammatory changes or certain inclusion bodies were encountered in sections from lungs, kidneys, bone marrow, upper part of the esophagus, tonsils, oral mucosa, tongue, skeletal muscle, spinal cord, lymphnodes, pituitary, thyroid, parathyroids, thymus, larynx, pancreas, umbilicus and umbilical vein or gastrointestinal tract, although mostly a large number of sections were prepared from various parts of these organs.

Virologic examination

Postmortem specimens from brain, liver and adrenals were obtained for virologic examinations and stored at − 70°. When the histologic studies revealed that the lesions probably were the result of a virus infection, samples were taken from the stored material. Ten per-cent suspensions were prepared from the three organs. The specimens were inoculated intracerebrally in mice and also on human embryonic lung tissue cultures, as well as on trypsinized human and monkey kidney tissue cultures. In baby mice and 4 week-old mice the brain and liver material gave signs similar to those given by herpes simplex virus. Brain material from mice with paralyses and suspected paralyses were subinoculated into other mice. These developed signs typical for the above-mentioned virus. In tissue culture characteristic cytopathogenic changes appeared 3 to 4 days after inoculation. Fluid from positive cultures were inoculated in mice and on the chorioallantoic membrane of 11 day-old embryonated eggs. The symptoms in mice and the pocks on chorioallantoic membrane were typical for herpes simplex virus. The specimens from the adrenals were negative in mice as well as in tissue cultures.

With fluid from positive human embryonic cultures and chorioallantoic specimens as antigens the suspected isolations of herpes simplex virus from brain and liver material could be confirmed by complement fixation tests.

Bacteriologic examination

With sterile technique samples were taken for bacteriology from the liver, adrenal, pancreas, spleen, kidney, colon, jejunum and from the left and right lower lobes of the lungs. Blood was drawn from the right atrium. In addition samples of peritoneal fluid, urine and cerebrospinal fluid were taken. The samples from the right atrium and from the lungs were taken with swabs after cauterization of the surface and the remaining pieces of tissue were flamed with alcohol before inoculation on media.

In all samples except from urine, *Staphylococcus aureus* (coagulase-producing and mannitol-fermenting) was cultured in varying amounts. Thus, rich growth was encountered in specimens from jejunum and the right lung, moderate growth in pieces from the pancreas, kidney and liver and sparse growth in cerebro-spinal fluid, ascites and blood. In addition, *E. coli* was cultured from adrenal, spleen and ascites. Enterococci were found in the colon. The staphylococci were sensitive to erythromycin (16 μg/cc) but resistant to sulfathiazole, penicillin, streptomycin, aureomycin, terramycin, chloramphenicol and achromycin. They were non-typable according to results with the phage-typing method. *Listeria monocytogenes* was not present. Inoculation on conjunctiva of guinea pigs was negative.

The pattern of resistance and the fact that the patient had spent her short life confined to the hospital made a cross-infection likely.

Comment

The results of the histologic and virologic studies are consistent with a diagnosis of a generalized herpes simplex infection. As evidenced from the findings of intranuclear inclusion bodies of Cowdry type A there was involvement of the esophagus, myocardium, liver, spleen, adrenals and brain. This generalized herpes virus infection was shown by bacteriologic studies to be associated with a staphylococcal septicemia.

Since there was no clinical or other evidence of infectious changes in the umbilicus, skin or the conjunctivae or within the lungs it is impossible to establish the portal of entry of the infectious agents with any certainty. However, the occurrence of an esophageal ulceration showing coagulation necrosis and intranuclear inclusions of adjacent cells is in accordance with the view that the esophagus was possibly the primary locus of the herpetic infection. Earlier, Zuelzer & Stulberg, and Le Tan Vinh, Alison & Lelong from the finding of herpetic esophagitis in cases of fulminant generalized herpes simplex in newborns have discussed the possibility of esophageal entrance of the infection. Other probable primary lesions which have been considered among the 13 cases of visceral herpes simplex in newborns which are reported (for references see reviews by Debré *et al.* and by Brain) are stomatitis (Pugh, Newns & Dudgeon) and keratoconjunctivitis (Zuelzer *et al.*).

In our patient the mother had no symptoms or signs of herpes simplex and no other source of the infection could be established. Unfortunately, serum for serologic studies was not available from the mother or the patient. In those cases reported earlier herpetic infection of the mother has been observed only in a few instances. Epstein & Crouch have described an infant of a mother with labial herpes simplex and McDougal, Beamer & Hellerstein another newborn of a mother with herpes simplex of the skin.

In the present case the association of a generalized herpes simplex and a staphylococcal septicemia is of particular interest. On the basis of the studies performed it is impossible to ascertain the site of entrance of the staphylococcal infection and whether the herpetic or the staphylococcal infection was primary. However, the finding of Gram-positive cocci in the tissue around the esophageal ulceration, which also contained cells with intranuclear inclusion bodies, is some support for the view that the staphylococcal and herpetic infection may have had the same primary focus.

With all probability the combination of a viral and a bacterial infection was the cause of the very rapid fatal outcome in our patient. It seems likely that the same type of double infection between herpes simplex virus and staphylococci as occurs in many cases of Kaposi's varicelliform eruption

(Ruchman & Dodd, and others) was one of the causes of the rapid deterioration of the patient. Such a theory gains support from the observation that Kaposi's disease may be complicated by generalized herpes simplex with adrenal necrosis (Brain, Pugh & Dudgeon), that is, the same visceral changes as those which were found in the probably first case of generalized neonatal herpes simplex described (Hass).

The fulminant course of herpetic infections in newborns has been a matter of confusion and many theories have been forwarded to explain this fact. The most commonly accepted one is that the immature tissue of the newborn is more susceptible to viral infections than the mature organs of later life. The case described in this study illustrates the importance of a concomitant bacterial septicemia as a contributing element resulting in a fulminant clinical course.

Summary

The clinical and autopsy findings in a female newborn infant who expired at an age of 15 days from a generalized herpes simplex infection associated with septicemia due to *Staphylococcus aureus* have been reported. The source of the herpetic infection which probably started as an ulcerative esophagitis remains unknown. The diagnosis of generalized viral infection was established from virologic studies of liver and brain tissue and from the demonstration of intranuclear inclusion bodies in the esophagus, myocardium, liver, spleen, adrenal glands and brain.

The interrelationship of generalized herpes simplex and staphylococcal septicemia is discussed, and the analogy to Kaposi's varicelliform eruption is considered.

Infection généralisée d'herpès simple associée à une septicémie staphylococcique chez le nouveau-né.

On a rapporté les recherches cliniques et celles faites à l'autopsie chez un nouveau-né de sexe féminin qui a expiré à l'âge de 15 jours par suite d'une infection généralisée d'herpès simple associée à une septicémie due au staphylococcus aureus. La source de l'infection herpétique qui commença probablement comme une œsophagite ulcéreuse reste inconnue. Le diagnostic de l'infection virulente généralisée fut établi en se basant sur des études virologiques du foie et du tissu cérébral, et sur la démonstration d'inclusions intercellulaires dans l'œsophage, le myocarde, le foie, la rate, les glandes surrénales et le cerveau. Le rapport réciproque entre l'herpès simple généralisé et la septicémie staphylococcique est discuté, et l'analogie avec l'éruption de Kaposi, ressemblant à la varicelle, est discutée.

Generalisierte Herpes simplex — Infektion verbunden mit Staphylokokken-Septikämie bei einem Neugeborenen.

Die klinischen und Sektions-Befunde eines weiblichen, neugeborenen Kindes, das im Alter von 15 Tagen zufolge einer generalisierten Herpes-simplex-Infektion verbunden mit einer Septikämie durch Staphylokokkus aureus ad exitum kam, wurden referiert. Der Ursprung der herpetischen Infektion, die wahrscheinlich als ulzeröse Oesophagitis begann, bleibt unbekannt. Die Diagnose der generalisierten Virus-Infektion stützte

sich auf virologische Untersuchungen der Leber und Hirngewebe sowie auf die Beobachtung intranukleärer Einschlusskörper in Oesophagus, Myokard, Leber, Milz, Nebennieren und Gehirn. Die gegenseitigen Beziehungen der generalisierten Herpes simplex-Erkrankung und der Staphylokokkenseptikämie wird diskutiert. Die Analogie zu Kaposi's varizelliformen Eruption wird in Erwägung gezogen.

Herpes simple generalizado asociado a una septicemia estafilocócica en un recién nacido.

Se han expuesto los signos clínicos y necrópsicos de una niña recién nacida que expiró a los 15 dias de vida con un cuadro de herpes simple generalizado asociado a una septicemia por estafilococo dorado. El origen de la infección herpética, que se inició en forma de una esofagitis ulcerosa, se desconoce. El diagnóstico de infección vírica generalizada se estableció por el estudio virológico del hígado y tejido cerebral, y por la demostración de cuerpos intranucleares de inclusión en el esófago, miocardio, hígado, bazo, suprarenales y cerebro. Se discute la relación entre el herpes simple generalizado y la septicemia estafilocócica, considerandose la analogía con la erupción variceliforme de Kaposi.

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PROGRESS IN PEDIATRICS

Extra-Colonic Manifestations in Chronic Ulcerative Colitis

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Extra-colonic lesions of varying types have frequently been described in chronic ulcerative colitis; for relevant references see (1, 11, 14). However, the pathogenesis of these lesions and their relation to the basic disorder has attracted but little interest.

The present report is based on the clinical findings with special reference to the occurrence of extra-colonic symptoms in patients with ulcerative colitis (u.c.) admitted to the Clinic during the last five-year period. The incidence of non-colonic manifestations in this material has been rather high and in many patients the clinical picture has been so bizarre and polymorphous as to suggest such diagnosis as disseminated lupus erythematosus, periarteritis nodosa or necrotizing angiitis.

The aim of the investigation has also been to compare the clinical features in patients with and without extra-colonic manifestations.

Material

The material consists of 48 children admitted to the Clinic during the period 1951–56. Thirty-four patients came from the Stockholm area, which usually furnishes the Clinic with patients, 14 have been sent from other districts. The material thus is somewhat selected. Twenty-four of the patients have shown extra-colonic manifestations presumably related to the colitis. In 24 patients no such manifestations have been demonstrated. In the 14 patients not living in the Stockholm area, extra-colonic lesions appeared in 5. The selection of the material thus has not influenced the incidence of complications.

The diagnostic criteria used are given in an earlier paper (11). In two patients, however, the roentgenological findings were essentially normal. Even in these cases the clinical and rectoscopical findings were, however, compatible with the diagnosis of ulcerative colitis. The diagnosis of non-specific, chronic, ulcerative colitis thus is well established in all patients.

TABLE 1

Comparison of patients with and without extra-colonic manifestations.

	Colitis without extra-colonic manifestations	Colitis with extra-colonic manifestations
Number of cases	24	24
Males	14	15
Females	10	9
Age at onset		
1–3 years	2	1
4–7 years	9	6
8–15 years	13	17
Observation time		
$< \frac{1}{2}$ year	2	1
$\frac{1}{2}$–2 years	14	7
2–4 years	3	8
$>$ 4 years	5	8
Course of the disease		
Progress	8	11
Status quo	8	11
Regress	2	2
Degree of invalidism		
None	11	7
For periods	12	8
Severe	0	5
Colectomy	2	5
X-ray findings		
Findings essentially normal	2	0
Parts of colon involved	8	7
Whole colon involved	14	17
Ileum involved	5	11
Blood transfusion given (no. of cases)	13	19
Complications observed (no. of cases)	2	9
Chamber eosinophil count		
$>$ 300 per mm^3	8	11
$<$ 300 per mm^3	3	4
Not performed	13	9

Table 1 (*continued*)

	Colitis without extra-colonic manifestations	Colitis with extra-colonic manifestations
Electrophoresis		
γ-globulin, g per 100 ml		
< 1.3	2	2
1.3–2.5	12	17
> 2.5	3	3
α_2-globulin, g per 100 ml		
< 0.6	1	2
0.6–1.0	8	10
> 1.0	8	9

Clinical Features and Laboratory Findings

Pertinent clinical data from this material are presented in Table 1. The patients with extra-colonic manifestations have on the average been observed for a longer period. Roentgenological changes in ileum were more common in the group with extra colonic manifestations. Invalidism also seemed to be more pronounced in this group. Wether these differences were related to the longer observation time cannot be decided. Reaction to blood-transfusions was more common in the complicated group. Most patients were anemic, reticulocytosis was a common finding. Coombs' test, which has been reported to be positive in some cases of ulcerative colitis (13), was negative in all 21 patients investigated. L.E. cells were searched for in 11 patients; in all these cases the phenomenon was lacking.

Total eosinophilic counts were performed in 26 cases, 20 of which were in excess of 300/mm^3; in several cases the counts varied between 1000 and 2000/mm^3. The Thorn-test was performed in 8 cases, with a normal response in all.

In 39 patients the concentration of different serum protein fractions was estimated by the use of paper electrophoretic technique. The values obtained are given in Table 1. In 35 of the cases the gamma-globulin concentration was moderately or markedly increased. The alpha$_2$-globulin concentration was high in 35 cases. There seemed to be no definite parallelism between the values of these protein fractions and the clinical state of the patient, the concentrations often being high even during remissions.

Specimens from the rectum were obtained by biopsy in 12 patients. Microscopic investigation revealed nonspecific acute and chronic infection. Vasculitis, although not of the type characteristic of periarteritis nodosa, was found in a single patient, who had no extra-colonic lesions.

TABLE 2

Survey of the different extra-colonic manifestations.

The connection with colitis was judged as uncertain when a common affection such as urticaria, stomatitis, conjunctivitis and angioneurotic edema appeared only on one occasion. The other complications judged as uncertain are discussed in the text.

Finding	Number of cases Relation to colitis	
	Probable	Uncertain
Skin involvement	8	3
Erythema nodosum	5	1
Necrotic ulcerations	4	
Butterfly rash	2	
"Spider"	1	
Urticaria		2
Stomatitis	3	3
Conjunctivitis		1
Angioneurotic edema	1	1
Arthralgia, hydrops	8	
Myalgic symptoms	2	
Endocarditis		1
Myocarditis		1
Liver damage	7	1
Erythrocyturia	8	1
Hemorrhagic disorder	3	

Survey of the Extra-colonic Manifestations

The different extra-colonic findings are listed in Table 2.

Skin.—Skin lesions appeared in 8 patients, some of them exhibiting several types of manifestations; in one case, for example, a butterfly rash, skin necroses and "spiders". Six patients had erythema nodosum; in one this might have been precipitated by penicillin. Skin involvement was in no case related to sulphamedication. In one patient erythema nodosum appeared after subtotal colectomy, but promptly disappeared after extirpation of the rectum.

Localized small areas of skin necrosis appeared in 4 patients. The lesions closely resembled papulonecrotic tuberculides and were usually localized to the extremities. Histological investigations in one patient revealed follicular hyperkeratosis of the same type as seen in various hypersensitivity disorders. For other details see Table 3.

Mucous membranes.—Acute ulcerative stomatitis was observed in 6 cases; in three, reactivation of stomatitis accompanied relapses of the colitis; in a

TABLE 3

Characteristics of the necrotic skin lesions.

Patient	Localization	Histological findings	Effects of cortisone	Culture
G. M.	Thigh	–	Probably good	–
H. S.	Legs, thighs	Perivascular infiltration of lymphocytes, the changes resembling those seen in folliculitis.	–	–
S. G.	Arms, buttocks, legs	Thickening of the vascular walls. Marked signs of vasculitis.	Good	Negative
B. H.	Trunk, buttocks, thighs	Slight follicular hyperkeratosis. Moderate perivascular infiltration mainly of lymphocytes. Changes as in folliculitis.	Good	Negative

fourth, this was associated with a severe conjunctivitis. In another three cases, the stomatitis occurred only once and the relation to the colitis was uncertain. Two of the latter cases had other forms of extra-colonic symptoms.

Angioneurotic edema.—One patient, 10 years of age, a few weeks after the onset of the colitis got a slight edema of the face. Acute laryngeal obstruction, developing one week later, necessitated tracheotomy. There were no other signs of catarrhal inflammation and the obstruction was probably due to angioneurotic edema localized to the larynx. It is worth mentioning that the patient developed the laryngeal edema and an obstructive type of jaundice the day after a blood transfusion complicated by fever and urticaria.

Joints.—Arthralgia or real polyarthritis, mostly with hydrops, was observed in 8 patients. Usually, the big joints were involved. The joint symptoms occasionally were associated with fever and exacerbation of the colitis. In no case did chronic joint changes with contractures develop. In two patients the joint symptoms dominated the early course of the disease and a preliminary diagnosis of rheumatoid arthritis was made.

Muscular involvement.—Myalgic symptoms with tenderness on palpation as well as spontaneous pains were observed in two cases in association with arthritis.

Cardiac involvement.—One of the patients with initial joint symptoms, developed aortic stenosis and insufficiency three years after the onset of ulcerative colitis. Whether this sequela after a carditic process was the result of rheumatic fever or some allied disorder or was connected with the colitis remains obscure.

TABLE 4

Survey of the cases with liver damage.

Jaundice was very slight in all but case R. E. The bilirubin values were usually not obtained when jaundice was at its highest intensity. Jaundice and liver enlargement were all transitory.

BSP = Sulfo-bromophtalein retention. Normal alkaline phosphatase activity with the method used (3) never exceeds 25 in the actual ages. ND = Not determined.

Case	Degree of severity of colitis before onset of jaundice	Jaundice	Enlarged liver	Serum bilirubin conc. mg per 100 ml		Alk. phosphatase activity units per 100 ml	BSP % retention after 30 min.
				Total	Direct		
450706 A. A.	−	+	+	2.0	ND	34	32
451007 R. E.	+ +	+	+	3.2	3.0	36	
440525 G. M.	+	+	−	0.9	0.6	27.5	
400407 P. M.	+	+	+	0.8	ND	51 20	0
430217 S. L.		?	−	1.1	0.7	75	4
380919 B. N.		−	−	0.5	ND	41	
470518 P. H. R.		−	−	0.4	ND	51	

Liver.—A survey of the cases with liver damage is given in Table 4. Liver function tests were not performed in every case. The bilirubin levels were not always determined when the jaundice was maximal. In patients with hyperbilirubinemia there was a direct Hijmans van den Bergh reaction as evidence of obstructive jaundice.

Case P. M. is of special interest. The initial symptoms were dominated by attacks of high fever and jaundice. Repeated blood cultures were negative. X-ray of the colon was normal. Because of the suspicion of biliary obstruction, laparatomy was performed 4 weeks after onset of the disease. The liver was markedly enlarged, the surface was even; beneath the capsulae there were hundreds of small, star-shaped grey-white areas. The glands of the portal hilus and the mesenterium were markedly enlarged. Culture from a liver biopsy specimen was negative. Histological investigations disclosed a slight portal cirrhosis, nonspecific inflammatory changes rich in eosinophiles and necroses of liver cells (Figs. 1 and 2). The symptoms of liver disease disappeared a few weeks after the laparotomy and during three years of observations there has been no return of such features.

Another patient, A. A., fell ill with fever and jaundice 9 months before definite symptoms of ulcerative colitis appeared. Whether the jaundice in this case was due to epidemic hepatitis or was connected with the ulcerative colitis as in case P. M., cannot be established.

Alkaline phosphatase activity was determined in 16 cases representing different stages of the disease. It was markedly increased in 6. Of these 6 patients, two had no other feature suggesting the occurrence of liver involvement or skeletal disorder, cf. Table 4.

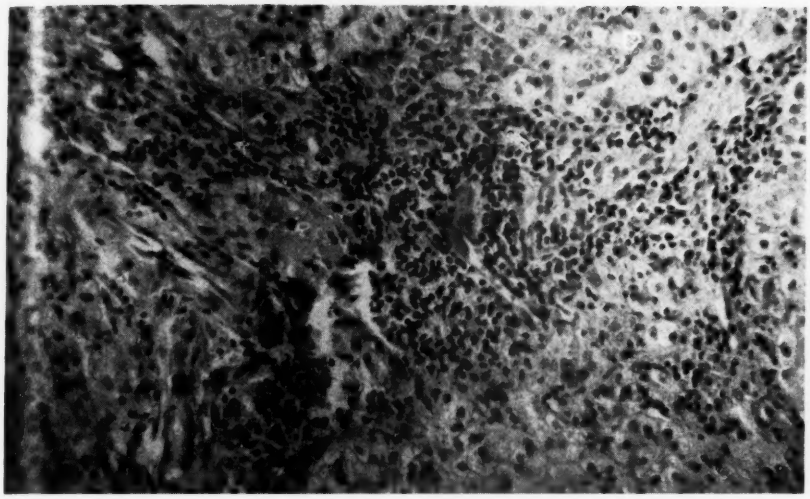

Fig. 1. Photomicrograph of liver biopsy specimen from the patient P. M. It will be seen that there is a localized area of inflammatory changes with infiltration of neutrophils and lymphocytes. The number of eosinophils was abundant. Htx-eos. Magnification × 100.

Kidneys.—Renal involvement was demonstrated in 8 cases. In five of these the only finding was a transient erythrocyturia with an Addis' count of more than 4 mill. red cells excreted in 12 hours. In the remaining three cases microscopic hematuria occasionally has been associated with albuminuria. Casts have not been demonstrated. There have been no signs of renal failure or hypertension.

Bleeding tendency.—Hemorrhagic symptoms have been obvious in three cases, two presenting subcutaneous hematomas, one with cerebral and massive gastrointestinal hemorrhage.

In one of these patients, a Schönlein–Henoch-like syndrome together with necrotic skin lesions was the first symptom of disease; in another, symptoms of anaphylactoid purpura appeared during the course of the chronic colitis.

The third case, one year after the onset of colitis, developed a hemophilia-like disease with prolonged clotting time (more than 25 minutes according to the method of Lee & White). The patient died from a cerebral hemorrhage before a complete investigation could be made, but it seems likely that the hemorrhagic disease was due to the presence of circulating anticoagulants.

Dental symptoms.—Thirty-three cases were investigated by a child psychiatrist. In none of these was the psychiatrist convinced that psychological

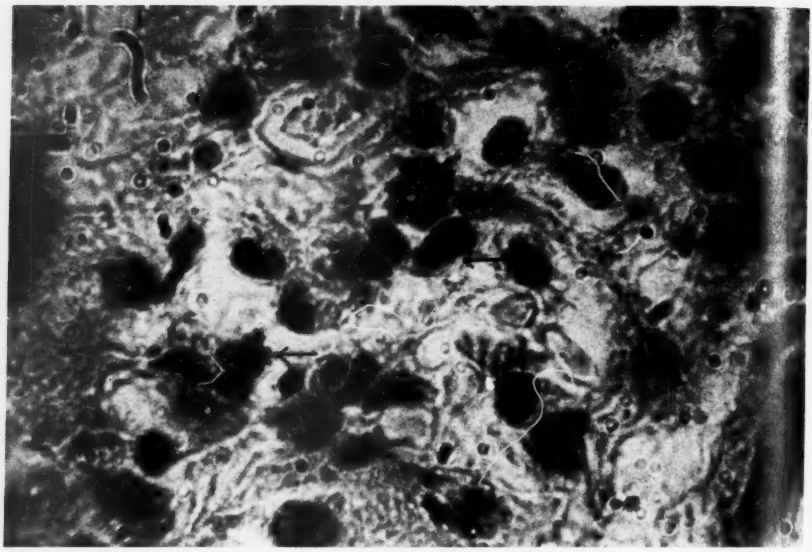

Fig. 2. Photomicrograph of liver section from the same patient as in Fig. 1. Htx-eos. Magnification × 600. Arrows indicate eosinophiles.

factors were of *primary* etiologic importance in the disease. One patient developed an atypical psychosis at the age of 17. Mental depression was common during exacerbations of the colitis.

Discussion

The early and sometimes simultaneous onset and the nonprogressive course of the extra-colonic manifestations is remarkable (Figs. 3 and 4). The question which arises is whether these manifestations are of toxic (infectious) origin or, more probable, if they develop as the result of allergic (hyperergic) reactions.

The most common manifestations—erythema nodosum and arthritis, as well as angioneurotic edema—are generally accepted as hyperergic reactions. Furthermore, the next common skin lesion—the ulcers—are more probably of hyperergic than of infectious origin. Repeated bacteriological cultures were negative, healing took place during cortisone administration and biopsy showed in one patient vascular lesions. The butterfly rash, which was observed in two patients, is usually associated with systemic lupus erythematosus, but may also be a nonspecific hyperergic reaction.

Aphtous stomatitis, which has been repeatedly described in ulcerative colitis (11, 14), may have the same pathogenesis as the skin lesions.

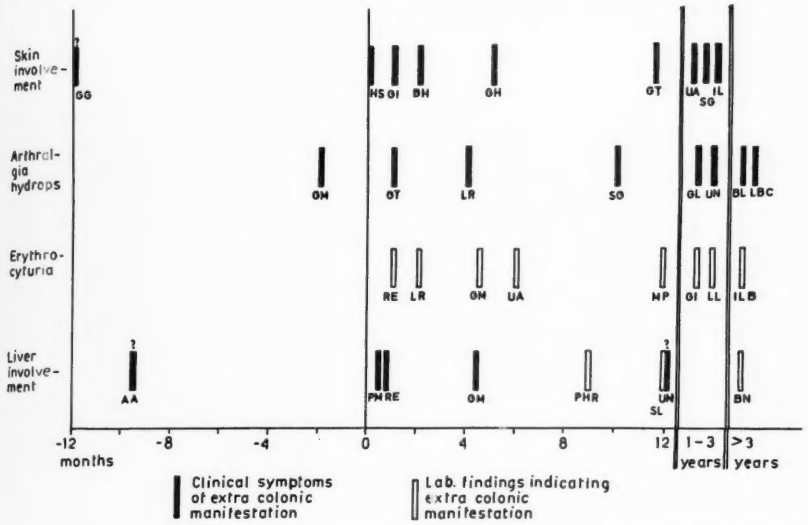

Fig. 3. The time of appearance of various extra-colonic manifestations in different patients with ulcerative colitis in relation to the start of clinical symptoms of the colitis. It will be seen from the figure that the extra-colonic manifestations in most patients have appeared after the lapse of a variable time after the onset of ulcerative colitis. However, in a few patients these symptoms have been obvious before the occurrence of symptoms of ulcerative colitis.

Hemorrhages of vascular origin can be of hyperergic nature, as demonstrated by Rice-Oxley & Truelove (14).

Myalgic symptoms which are common in different hyperergic diseases, have been reported in a patient with ulcerative colitis. These symptoms may be due to inflammatory and vascular lesions as revealed in the findings in muscle biopsy specimens (17).

Heart lesions have been described in u.c. (1), but seem to be uncommon. Whether the valvular disease in our patient G. T. was associated with the colitis or was the result of a carditis of another etiology remains obscure. It might, however, have its origin in a mural endocarditis as seen in Libman–Sacks syndrome (16).

Fatty degeneration has characterized the liver lesions most often observed in u.c. (5, 9, 10, 11). The changes seem to be of toxic-infectious origin though the anemia and malnutrition may be contributory. The course of the liver disease has in some cases been progressive and liver damage has been regarded as a sign of an unfavourable prognosis (7, 11). In our series there are, however, several cases which do not fit into this description. The early onset of hepatic lesions (in some cases, before any severe intestinal symptoms), the nonprogressive course, the transient high serum-level of conju-

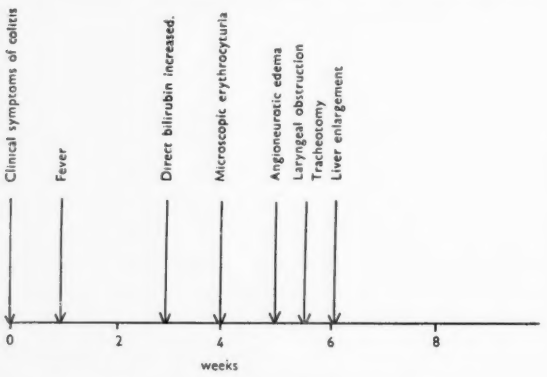

Fig. 4. The time of appearance of various extra-colonic manifestations in one patient with ulcerative colitis (R. E.). It will be seen from the figure that there were rather short intervals between the start of the colitis and the appearance of symptoms from other organs.

gated bilirubin and elevated alkaline phosphatase activity may suggest some other type of lesion than fatty degeneration ending in cirrhosis. Inability to correlate the course of the basic disease, e.g. ulcerative colitis with hepatic findings has been noted by others (5, 12). Transitory embolic involvement of the liver has been suggested as a causative factor (9). The exact pathogenesis of the liver lesions in our cases cannot be ascertained. We believe, however, that they resemble the lesions seen in some chronic hypersensitivity disorders and can hardly be explained as a toxic-infectious reaction only.

Reports on renal lesions in u.c. are sparse (7). This may partly be due to the method of investigation. Only repeated quantitative examinations of the urinary sediment revealed significant findings in some patients. The cause of the microscopic hematuria (and albuminuria in some patients) is obscure, but it does not seem improbable that hyperergic factors are operative as in anaphylactic purpura. Hypovitaminosis C due to a malabsorption syndrome does not seem a probable cause, since all our patients were on an ordinary diet rich in vitamins and were given extra multivitamin preparations. More likely, the pathological changes responsible for albuminuria and erythrocyturia are endothelial proliferations of the glomeruli which, according to Jones, Baggenstoss & Bargen, may occur in some patients with u.c.

The view that most of the extra-colonic manifestations which may appear during the course of u.c. develop as the result of hyperergic reactions is supported by the high incidence of eosinophilia and elevated serum gammaglobulin concentration in patients suffering from this disease (Table 2). On the other hand, hypergammaglobulinemia which was found in nearly all our patients may also be due to liver damage which, as evidenced from the histological investigation of biopsy or autopsy specimens of a large series of u.c., is present in about 40 per cent of all cases (8). Since, however, the liver changes most commonly found are characterized by fatty infiltration, a condition

which does not give rise to alterations of the albumin/globulin ratio, it seems unlikely that liver cell damage is the main cause of hypergammaglobulinemia in u.c. Since the gamma-globulin fraction mainly or purely consists of antibodies, an elevation of this fraction very probably may arise as a response to abnormally intense antigenic stimulations, the antigenic substances being absorbed from the diseased colon. In this connection the question whether hypersensitivity reactions are responsible for the development of the whole syndrome of u.c. may be considered. The favorable response to cortisone treatment as well as the observation of Elchlepp & Kirsner that it is possible to produce colon lesions resembling those seen in u.c. in rabbits following auto-immunization procedures is in harmony with such a hypothesis.

Ulcerative colitis has been described in a patient with systemic lupus erythematosus (2). As already stressed, the differential diagnosis may be difficult. Periarteritis nodosa (15) necrotising angiitis (17) or butterfly rash cannot be accepted as proof that u.c. is a "systemic" disease. These manifestations probably are nonspecific hyperergic reactions. From a practical point of view it is important to realize that the extra-colonic lesions in u.c. disappear if the colon (and if necessary the rectum) are removed. In our experience an increasing number of patients with u.c. are undergoing ileostomy and colectomy (plus, if necessary, extirpation of the rectum) since they cannot be controlled by medical treatment (12). The appearance of cancer in long-standing cases is another indication for surgical treatment (12). Finally we want to stress that there seems to be no difference regarding course or prognosis between cases with and cases without extra-colonic manifestations.

Acknowledgements

We are greatly indebted to Dr. E.-B. Nordlund who has carried out a psychiatric study in our patients with u.c. We also owe gratitude to Dr. H. Gentele for histological examination of skin biopsy specimens and to Dr. B. Ivemark for the investigation of rectal biopsy specimens.

Summary

The various extra-colonic manifestations observed in 24 out of 48 children with ulcerative colitis have been described. Most of these changes may most likely be the result of hyperergic reactions, probably due to hyperimmunisation. Such a view is supported from the occurrence of very high serum-levels of gammaglobulin in patients with u.c. The extracolonic manifestations seen in u.c. are similar to those seen in such connective tissue disorders as systemic lupus erythematosus and periarteritis nodosa. The extra-colonic manifestations disappear after colectomy (and if necessary rectum extirpation) and their occurrence does not seem to contraindicate surgical intervention.

Manifestations en dehors du côlon dans la colite ulcéreuse chronique.

On décrit les différentes manifestations en dehors du côlon observées chez 24 sur 48 enfants avec une colite ulcéreuse. La plupart de ces changements peuvent, selon toute probabilité, être le résultat de réactions hyperergiques, dues probablement à une hyper-immunisation. Une telle opinion est soutenue à cause de la présence de taux de sérum très élevés de gamma-globuline chez les malades avec une colite ulcéreuse. On a souligné l'analogie des caractéristiques cliniques constatées dans la colite ulcéreuse, compliquées par différentes manifestations en dehors du côlon, et celles observées dans des troubles de tissu conjonctif, tel que le lupus érythémateux systémique et la périartérite noueuse. Les manifestations en dehors du côlon disparaissent après une colectomie (et éventuellement l'extirpation du rectum), et leur apparition ne semble pas être une contre-indication pour une intervention chirurgicale.

Ausserhalb des Colon gelegene Manifestationen bei chronischer Colitis ulcerosa.

Verschiedene ausserhalb des Colon gelegene Manifestationen — bei 24 von 48 Kindern mit Colitis ulcerosa — wurden beschrieben. Die meisten dieser Veränderungen sind höchstwahrscheinlich das Resultat hyperergischer Reaktionen, vielleicht zufolge Hyperimmunisation. Diese Ansicht ist durch das Auftreten von sehr hohen Serum-Gammaglobuline-Spiegeln, die man bei solchen Patienten findet, gerechtfertigt. Der Artikel betont die Ähnlichkeit der klinischen Merkmale zwischen der Colitis ulcerosa einerseits — kompliziert durch verschiedene ausserhalb des Colon gelegene Manifestationen — und der zu beobachtenden Bindegewebszerstörung bei systemisierten Lupus erythematosus oder bei Periarteritis nodosa andererseits. Die ausserhalb des Colon gelegenen Manifestationen verschwinden nach Colectomie (und evtl. Rectumexstirpation); ihr Auftreten lässt chirurgisches Eingreifen nicht kontraindiziert erscheinen.

Manifestaciones extracólicas de la colitis ulcerosa crónica.

Se han descrito las diversas manifestaciones extracólicas observadas en 24 niños, pertenecientes a un grupo de 48 enfermitos con colitis ulcerosa crónica. La mayor parte de estas manifestaciones son probablemente consequencia de reacciones hiperérgicas por hiperinmunización. Este criterio se apoya en la aparición de cifras muy elevadas de globulinas gamma en el suero de los pacientes con c.u. Se han puesto en evidencia las analogias que existen entre el cuadro clínico de la colitis ulcerosa complicada con diversas manifestaciones extracólicas, y el de las enfermedades del colágeno, como el lupus eritematoso sistematizado y la periarteritis nodosa. Las manifestaciones extracólicas desaparecen con la colectomía (y eventualmente la ablación del recto) y su aparición no parece contraindicar la intervención quirúrgica.

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PROGRESS IN PEDIATRICS

Paediatric Aspects of Brain Tumors in Infancy and Childhood

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Early diagnosis of brain tumors in infants and young children is often difficult. Lack of cooperation from the side of the child at examination, scarcity of localizing neurological manifestations and misinterpretation of important symptoms, e.g. vomiting, contribute to this. Furthermore, the general practitioner as well as the paediatric specialist seldom obtain more than a limited experience of these cases. In paediatric clinics infants and children with brain tumors constitute a relatively small minority of the patients admitted for neurological examination. It would thus be understandable if the diagnosis of brain tumors at least in the younger paediatric age group sometimes should be delayed. The primary diagnosis of an intracranial tumor in childhood is no doubt the task of the paediatrician and it was thus thought of interest to know to what extent diagnostic errors occur in paediatric clinics and the possible consequences of such mistakes. Most of the investigations concerning brain tumors in children have been carried out by neurosurgeons and the present study is an attempt to discuss some problems from paediatric point of view.

Roentgenographic changes, surgical treatment, operative mortality and tumor pathology will not be discussed in any detail. For this and for references to the literature the reader is referred to the monographs by Bailey *et al.* and by Ingraham & Matson and to a recent paper by Odom *et al.*

Materials

The case records at the four Paediatric Clinics, the Hospital for Epidemic Diseases, the Neurological Clinic and the two Neurosurgical Clinics in Stockholm for the 10-year period from 1947 through 1956 were reviewed. Only Swedish patients were considered and no children older than 15 years when symptoms first appeared were included. In the series were included the total number of children in the city of Stockholm diagnosed as cases

of brain tumor during this period. It was thus possible to get information of the incidence of brain tumors in the paediatric age group in the city of Stockholm.

Orbital tumors, abscesses, subdural haematomas, arachnoid and other cysts and vascular malformations were not included in the study. Vascular malformations such as arterio-venous aneurysms, Sturge–Webers syndrome and arterial aneurysms were found only in a few cases.

The case records of the patients diagnosed in the Paediatric Clinics were reviewed in more detail in order to get, *inter alia*, an impression of the diagnostic procedures employed.

The case records of children admitted to the four Paediatric Clinics with a diagnosis of suspected brain tumor were also studied in order to elucidate how often the diagnosis of the referring physican was verified. It is possible that not all of these patients were found as they were registered under various diagnosis. The presence of brain tumor was excluded in most of these cases already by the examination. Whenever a slight suspicion of brain tumor remained after the patients had left hospital a follow up was made. As the observation time in most of these cases was sufficiently long it is not very likely that any cases of brain tumor were included in this group by mistake.

When a statistical evaluation of the result was made a significance level of three times the standard error was used.

Results

During the 10-year period 1947–1956 293 patients 15 years old or less were treated for brain tumor at the hospitals previously mentioned. In the great majority of these cases the diagnosis were verified by operation or by post mortem. Of the cases not verified (45 patients) about half were diagnosed as supratentorial and half as infratentorial tumors.

The type of tumor and incidence at different ages are shown in Figs. 1 and 2. As the present series seems to be in good accordance with previous reports only a few comments will be made.

The most prominent symptoms, the duration of the histories and the results of the treatment will be briefly mentioned. For each tumor group the number of patients still living after a certain period of observation, varying from half a year to 10 years, is given. When not otherwise stated the rest of the patients was known to be dead.

For each group of tumor is given the number of patients who during their illness had been treated with an other diagnosis than brain tumor. In the Neurosurgical Clinics were treated 275 patients. These were with a few exceptions referred from childrens hospitals (204 cases) or other hospitals (63 cases).

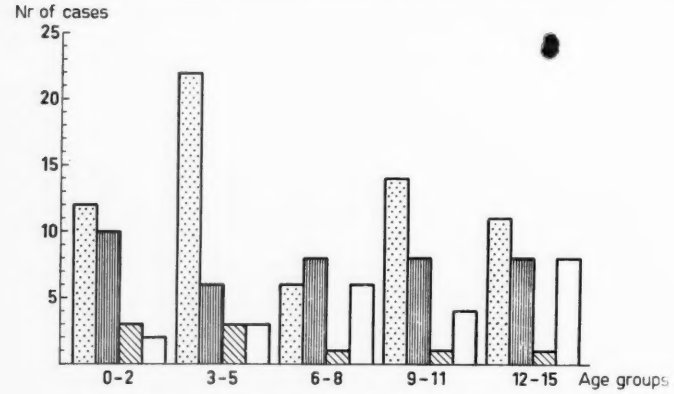

Fig. 1. Age distribution of 137 supratentorial tumors.

Gliomas . . . . . 65 cases
Craniopharyngiomas, pinealomas and teratomas . 40 cases
Miscellaneous . . . . . 9 cases
Not verified . . . . . 23 cases

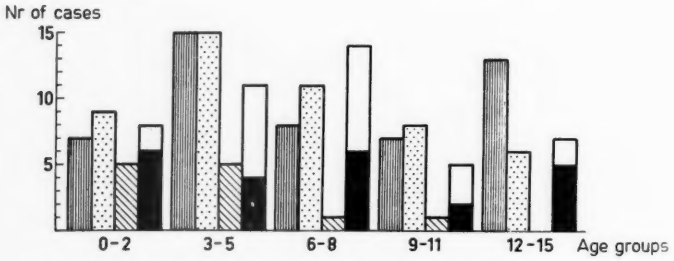

Fig. 2. Age distribution of 156 infratentorial tumors.

Astrocytomas . . . . . 50 cases
Medulloblastomas . . . . . 49 cases
Ependymomas . . . . . 12 cases
Gliomas of the brain stem . . . . . 23 cases
Not verified . . . . . 22 cases

Verified Supratentorial Tumors—114 Cases

Of the patients with verified supratentorial tumors 71 were boys and 43 girls.

Gliomas of the hemispheres (21 boys, 13 girls).—The different types of tumor are shown in Table 1. The most common symptoms were convulsions, hemiparesis, headache and emotional disturbances. Papilloedema was present in $\frac{2}{3}$ of the cases. The average duration of the histories was 5 months

TABLE 1

Different types of gliomas localized to the hemispheres or midline structures.

Tumor	Hemisphere	Midline
Astrocytomas	17	6
Ependymomas	8	4
Glioblastomas	8	8
Oligodendrogliomas	1	1
Total	34	19

(10 days to 2 years) in 29 cases and 7–8 years in three cases with epileptic seizures and astrocytomas. All were operated upon except two newborns, who died a few days post partum. Eighteen patients were living half a year to 10 years postoperatively (average 3½ years).

Thirteen patients had been hospitalized previously with other diagnosis than brain tumor. Six had been regarded as epilepsia, two as "vomiting", two as encephalitis and three cases had other diagnosis.

Gliomas in midline structures (12 boys, 7 girls).—The different types of tumor are shown in Table 1. In these cases the symptoms usually progressed more slowly and were chiefly signs of increasing intracranial pressure. In 16 cases the average duration of the histories was 7 months (10 days to 2 years). Two patients with endocrine symptoms had very long histories, 4 and 7 years respectively. One child died during the neonatal period. Seventeen patients were operated upon. Three were living 4 to 8 years after operation.

Five patients had previously been hospitalized with other diagnosis than brain tumor.

Gliomas of the optic chiasma and intracranial part of the optic nerves (7 boys, 5 girls).—All of these patients were less than 10 years old. Common symptoms were visual disturbance, headache, vomiting, somnolence and endocrine manifestations. In eleven cases the average duration of the history was 7 months (2 months to 2½ years) and in one case more than 3 years. Five patients were living one to 4 years after operation.

Two patients had previously been treated in hospitals, one as encephalitis and one as neurofibromatosis.

Pinealomas and teratomas of the pineal region (12 boys, 2 girls).—The pineal region has been defined according to Ringertz *et al.* (1954). Seven of the boys had pinealomas, 3 highly differentiated teratomas and 2 undifferentiated teratoid tumors. Both girls had pinealomas. Ten of these children were more than 10 years old when the diagnosis was made. The

symptoms usually appeared suddenly with headache, vomiting, drawsiness and gait disturbances. Ocular symptoms were common and pronounced papilloedema was the rule when the diagnosis was established. Two cases had diabetes insipidus. None had shown signs of precocious puberty. The average duration of the case histories was 4½ months (one to 9 months). Exstirpation of the tumor was made in 12 cases and of these 2 were living 4 and 10 years respectively after the operation. One boy lived 3½ years after palliative surgery and X-ray treatment. One child died before operation was made.

All of these patients had been regarded as brain tumors when first examined in hospital.

Craniopharyngiomas (7 boys, 7 girls).—All of these patients were less than 11 years old when the diagnosis was made. Dominating symptoms were visual disturbance and paroxysmal headache. Opthalmoscopic findings were rather variable, varying from slight papillar atrophy to pronounced papilloedema. The average duration of the histories was in 11 cases 5½ months (one month to one year). Two patients had headache for 5–6 years. One infant died during the neonatal period. More or less radical exstirpation was performed in 11 cases and cyst-tapping in 2 cases. Five children were living one to 3 years postoperatively. Two patients had not been followed.

Four of these patients had before admission been treated for headache, vomiting and/or failing vision without suspicion of brain tumor.

Other teratoid tumors (8 boys, 4 girls).—Eight tumors were localized to the hemispheres and had a very variable histological structure. Symptoms and duration of the case histories varied. In 6 patients the symptoms had appeared already during infancy. All were operated upon. Two patients were still living 4 and 5 years after operation.

In 4 cases the tumor had a suprasellar localization. These children had diabetes insipidus as an early and dominating symptom and had previously been in hospital with this diagnosis. The tumors were histologically regarded as pinealomas. None of the 4 patients survived the operation more than one year.

Miscellaneous tumors.—In addition to the groups mentioned above there were in the material 3 ventricular papillomas, 2 meningeomas, 2 meningeal melanosarcomas, 1 neurinoma and 1 tuberculoma. Two patients had been in hospital with other diagnosis.

Not Verified Supratentorial Tumors—23 Cases

Of the patients with not verified supratentorial tumors 16 were boys and 7 girls.

"*Central gliomas*" (14 boys, 7 girls).—The diagnosis was based on the clinical and radiological findings. At examination there were signs of an expanding lesion in the midline structures especially in the vicinity of the hypothalamic area and the third ventricle. The case histories were of two types. In about half of the patients (11 cases) the histories were short with an average duration of 3 months (2 days to 10 months) and dominated by intermittent symptoms of increased intracranial pressure. The other half of these patients had much longer histories with an average duration of 4½ years (1½ to 10½ years) with endocrine symptoms (e.g. diabetes insipidus and precocious puberty), failing vision and mental disturbances as the most important manifestations. Later on these patients often developed signs of rapidly increasing intracranial pressure and in both groups of patients papilloedema was the rule when the diagnosis of brain tumor was made These patients were treated with palliative operations or by X-ray and 17 cases were living one to 10 years after the diagnosis was established.

It is likely that most of these neoplasms are slowly growing teratoid tumors or tumors belonging to the histologically and clinically benign astrocytomas which by Ringertz & Nordenstam have been labelled "cerebellar".

Eight of these children had been treated during their illness in other hospitals without suspicion of brain tumor.

"*Pinealomas*" (2 boys).—Two boys had clinical and radiological signs of a tumor in the pineal region. Both died within 8 months after palliative operation.

Verified Infratentorial Tumors—134 Cases

Of the patients with verified infratentorial tumors 78 were boys and 56 girls.

Astrocytomas of vermis and cerebellar hemispheres (28 boys, 22 girls).—Main symptoms were headache, vomiting, sixth-nerve paralysis and "cerebellar symptoms". An intermittent course with remission was common. Papilloedema was present in almost all cases when diagnosis was established. Average duration of the case histories was 7 months (2 weeks to 3 years). All patients were operated upon and 33 lived half a year to 10 years after operation. One patient had not been followed.

Five patients had previously been hospitalized with other diagnosis (cerebral palsy, 2 cases; postencephalitic sequelae, 2 cases; hydrocephalus, 1 case).

Medulloblastomas in the region of the roof of the fourth ventricle (27 boys, 2[illegible] girls).—The symptoms were much of the same type as in the foregoing group but more steadily progressive and the average duration of the histories was shorter, 3 months (10 days to one year). Papilloedema was

present in practically all cases. All but three patients were operated upon. Most of the patients had X-ray treatment postoperatively. In two cases the survival period was 6 and 7 years and three other patients lived more than 2 years.

Five of these patients had previously been treated for "psychogenic" vomiting and a 13-year old girl had been diagnosed as a case of disseminated sclerosis.

Ependymomas of the fourth ventricle (10 boys, 2 girls).—The clinical picture was of the same type as in the foregoing group and the average duration of the case histories was 3 months (one to 11 months). All of the patients had papilloedema. All were operated upon. One patient was still alive 6½ years after the operation. Most of these patients received X-ray treatment postoperatively.

All cases in this group had been regarded as brain tumors when first examined.

Gliomas of pons and medulla oblongata (13 boys, 10 girls).—In this group were also included astrocytomas, medulloblastomas and ependymomas originating from the floor of the fourth ventricle. Vertigo, diplopia, mental symptoms, "crossed hemiplegia" and later on bilateral paralysis of the bulbar muscles and limbs dominated. Headache, vomiting and papilloedema were less prominent signs. In 21 cases the average duration of the case histories was 2½ months (one to 5 months) and two patients had symptoms more than one year. The tumor was explored in 10 cases. One boy was still living 2½ years after operation. Like several of these patients he had been treated by X-ray. One patient was not followed.

Five children had previously been treated in other hospitals with no definite diagnosis established.

Not Verified Infratentorial Tumors—22 Cases

Of the patients with not verified infratentorial tumors 7 were boys and 15 girls. The diagnosis was in all cases "brain stem glioma" and was based on clinical and radiological symptoms of an expanding lesion in the brain stem. The average duration of the case histories was 3 months (10 days to one year). Most of these cases received X-ray treatment. Nineteen patients were dead and in 18 cases the exact date of death was known. The average survival period was in 17 cases 3½ months (2 days to 7 months) after diagnosis had been established. An 8-year old girl lived 2 years after an intensive X-ray treatment. One child was still alive 1½ years after diagnosis. The fate of two patients was unknown.

Five children had previously been treated in other hospitals, two as encephalitis, one as poliomyelitis and one child had the diagnosis "ataxia".

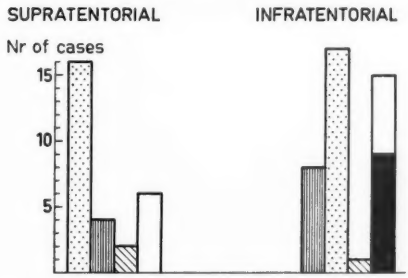

Fig. 3. Number and different types of brain tumor in children admitted to the paediatric clinics in Stockholm 1947–1956 (69 cases).

Supratentorial tumors, 28 cases

Gliomas . . . . . .
Craniopharyngeomas, pinealomas and teratomas . . . . . .
Miscellaneous . . . . . .
Not verified . . . . . .

Infratentorial tumors, 41 cases

Astrocytomas . . . . . .
Medulloblastomas . . . . . .
Ependymomas. . . . . .
Gliomas of the brain stem . . . . .
Not verified . . . . . .

Among the patients of the present communication four were *newborns* who died a few days after delivery. Two had hemispheral gliomas, one had a glioma of the quadrigeminal plate and one patient had a craniopharyngioma. In seven cases symptoms were observed during the neonatal period. One patient had a glioma of the basal ganglia, two had hemispheral teratomas, two had medulloblastomas of the fourth ventricle, one had an astrocytoma of the vermis and one had a brain stem glioma.

Patients of the Paediatric Clinics

During the ten-year period 1947–1956 69 children with brain tumors were admitted to the Paediatric Clinics in Stockholm. The diagnosis were later on verified in either of the neuro-surgical departments or by post mortems. In twelve cases, chiefly supratentorial tumors and "gliomas" of the brain stem, the diagnosis was not verified histologically but must from a clinical and roentgenological point of view be regarded as reasonably safe. The number of the different types of tumor is given in Fig. 3. As could be expected this material shows the same relation of supratentorial tumors to infratentorial as the total material. The supratentorial tumors were 28 (41 per cent) and the infratentorial 41 (59 per cent). Twenty-five per cent were medulloblastomas against 17 per cent in the total series.

The more important symptoms as given in the case histories of these

TABLE 2

Incidence of early prominent symtoms and initial symptoms in 69 children with brain tumor.

(28 supratentorial and 41 infratentorial tumors.)

Symptom	Supratentorial		Infratentorial	
	Number of cases	First symptom in	Number of cases	First symptom in
Headache	12	4	23	7
Vomiting	13	4	31	17
Mental symptoms	7	4	16	1
Failing vision or defects of visual fields	4	2	3	1
Hemiplegia and allied signs of lesions of the pyramidal tract	8	2	7	—
Sixth nerve paralysis	4	—	18	10
Palsy of other bulbar nerves	—	—	6	1
Convulsions	7	5	—	—
Disturbance of coordination	4	—	24	2
Enlargement of the head	9	4[a]	4	1
Dizziness	2	—	1	1
Endocrine symptoms	4	3	—	—

[a] Newborns.

69 patients are presented in Table 2. It must be noted that generally the appearance of the initial symptom was accurately stated but in the cases with infratentorial tumors it was often not possible to decide which symptom, headache or vomiting, that had appeared first. Often both had apparently been observed at the same time. Mental changes were chiefly described as irritability, drowsiness, lassitude and apathy. Of the patients with endocrine symptoms two had diabetes insipidus, one was dwarfed and one had precocious puberty.

The eye-grounds were examined by ophthalmologist in 60 cases (infratentorial tumors 39, supratentorial 21). Papilloedema was found in 25 patients with infratentorial and in 12 patients with supratentorial tumor. Optic atrophy was demonstrated in 6 cases (3 with supratentorial and 3 with infratentorial tumor). Of the eleven patients with infratentorial tumor and normal eye-grounds 9 had gliomas of the brain stem.

Abnormal oto-neurological findings were present in 10 patients with infratentorial tumors but the investigation was made only in 20 cases of infratentorial and in 3 cases of supratentorial tumor.

TABLE 3

Result of electroencephalography in 39 cases of brain tumor.

Borderline findings imply slight to moderate, generalized, nonspecific dysrhythmia.

EEG findings	Supratentorial tumors in Midline structures	Supratentorial tumors in Hemispheres	Infratentorial tumors
Normal	1	—	7
Borderline	1	—	8
General marked dysrhythmia	4	—	9
Paroxysmal bilateral discharges	2	—	—
Focal abnormalities or marked hemispheral asymmetries	—	7	—
Total	8	7	24

Routine roentgenographic examination of the skull was made in 50 patients and abnormalities were found in 21 cases. The lesions demonstrated were chiefly signs of increased intracranial pressure and intracranial calcifications.

Electroencephalography was made in 39 cases. The results are shown in Table 3.

Pneumoencephalography or ventriculography were performed in 18 cases. Abnormalities were demonstrated in all of these cases.

The 69 patients with brain tumor were referred to the Paediatric Clinics with various diagnosis. Twenty-seven patients were referred as cases of brain tumor. In Table 4 are shown the diagnosis at admission.

Eighteen patients of the 27 referred with a diagnosis of brain tumor had an infratentorial and 9 had a supratentorial tumor. Twenty-three of the 42

TABLE 4

Diagnosis at admission to the Paediatric Clinics in 69 cases of brain tumor.

Diagnosis	Number of cases	Diagnosis	Number of cases
Brain tumor	27	Vomiting	4
»Neurological investigation»	6	Epilepsia	3
Headache	5	Ocular muscle palsy	3
Encephalitis	5	Hydrocephalus	3[a]
Endocrine disorder	5	Miscellaneous	9

[a] Newborns.

TABLE 5

Number of patients with brain tumor referred to the Paediatric Clinics with this diagnosis or with other diagnosis.

Referred by	Number of patients with diagnosis of brain tumor	Number of patients with other diagnosis
Private practitioner	4	15
Outpatient department	10	17
Other children's hospital	6	4
Other hospital	7	6
Total	27	42
Average duration of history	3.6 months	5.5 months
Average age at admittance	6.5 years	4.6 years

patients referred with other diagnosis had an infratentorial and 19 had a supratentorial tumor. These figures roughly correspond with the distribution of infra- and supratentorial tumors observed in the total number of patients admitted to the Peadiatric Clinics with brain tumor. The number of infratentorial tumors (18 cases) correctly diagnosed before admission as brain tumors is possibly somewhat higher than could be expected from this distribution but the difference is hardly significant.

The 69 patients with brain tumor had previously been seen by private practitioners or had come directly to the outpatient departments. Several patients were referred from other hospitals. As seen from Table 5 the private practitioners had in a considerable number of cases (15 out of 19) not suspected a brain tumor. The corresponding figure for the outpatient departments is somewhat lower. The average duration of history and the average age of these patients at admission is also given in the table.

It was thought of interest to compare the patients with brain tumor with patients referred to the Paediatric Clinics with a suspicion of brain tumor during the same ten-year period. Sixty-one patients were found and their final diagnosis were registered. Prominent symptoms suggesting a brain tumor were present in many cases e.g. papilloedema in 21 patients. Fifteen patients had such cerebral lesions (congenital malformations and degenerative disorders) that a suspicion of brain tumor was very natural and in most of these patients the final diagnosis was established only after very comprehensive examinations or a period of observation or in some cases by post mortems. In 17 patients the final diagnosis was epilepsia, 10 had headache the nature of which could not be exactly defined and 6 patients had enc-

TABLE 6

Number of patients referred with a suspicion of brain tumor but with other final diagnosis (61 cases)

Referred by	Number of patients
Private practitioner	12
Outpatient department . . .	20
Other children's hospital . .	27
Other hospital	2

phalitis. The rest, 13 cases, had miscellaneous diagnosis. As seen from Table 6 the largest group of these patients came from other childrens hospitals but a considerable number were referred by private practitioners and the outpatient departments.

During the 10-year period from 1947 through 1956 fifty-five patients with brain tumor belonging to the paediatric age group were diagnosed in the city of Stockholm. Thirty-one children had supratentorial and only twenty-four infratentorial tumors. The corresponding figures for the County of Stockholm were twelve and eighteen respectively.

The number of children less than 15 years old in the City of Stockholm increased from 128,891 in 1947 to 166,903 in 1956. The annual incidence of brain tumors during this period and in this age group was rather variable, varying from one case in 1951 to ten cases in 1949. The average annual incidence was 0.036 per mille. In other words each year 3–4 new cases of brain tumor will be expected in 100,000 children less than 15 years old.

Comment

The present series of brain tumors shows in good accordance with earlier reports that the majority of tumors observed in children is gliomas (80 per cent of the verified tumors of the present series). Meningiomas, neurinomas of the acoustic nerves and pituitary tumors are very rare. Infratentorial tumors are more common than supratentorial. In the present series the infratentorial were 54 per cent and the supratentorial 46 per cent of the verified tumors. Brain tumors are in children usually localized to midline structures. This was the case in 83 per cent of the verified tumors of the present series. Signs of increased intracranial pressure and a relative lack of localizing neurological symptoms are thus characteristics of brain tumors in the paediatric age group. On the other hands, important symptoms such as headache and vomiting are not always present when diagnosis is estab-

lished. Absence of these symptoms was observed particularly in patients with gliomas of the brain stem.

In the group of children with brain tumor examined in the four Paediatric Clinics of Stockholm (69 cases) the number of medulloblastomas appeared higher than in the total series. The difference is not very large and could not be found to be significant. As a whole this group may be regarded as a representative sample of the total series.

Fifty-five children belonged to the City of Stockholm and in this group the supratentorial tumors were, somewhat unexpectedly, in the majority. The higher incidence of supratentorial tumors is, however not significant when compared with the total series.

It is well known and is also demonstrated by the present communication that in the majority of children with intracranial tumors the outlook is not favourable. Two groups of tumor, the cerebellar astrocytomas, and some types of glioma of the cerebral hemispheres make exceptions to this rule. Judging from the present series the neoplasms labelled "central gliomas" in this paper also appear to have a relatively good prognosis. The important question is whether earlier recognition would improve the prognosis of brain tumors in the paediatric age group. It is obvious that the localization and biological type of certain tumors make a radical treatment impossible at present, irrespective of an early or late diagnosis, e.g. gliomas of the brain stem. In other cases a delay of diagnosis may be important and influence the result of surgery.

It is no doubt in many cases a delicate task to decide from data collected in case notes whether diagnostic mistakes were made or not. Symptoms which at the time, when the case notes were written clearly indicated an expanding intracranial lesion may a few months previously have appeared less important. It was nevertheless thought of interest to learn to what extent patients with a final diagnosis of brain tumor previously during their illness had been regarded as having other diseases than brain tumor. It was usually not possible from the data available to decide whether this had happened at the stage when the patient was seen by a private practitioner. Most of the patients with other diagnosis had, however, been examined in hospitals. The total number of patients was 293 and of these about 20 per cent had during their illness been treated with other diagnosis.

It may be of interest to note that the highest incidence of such "possible diagnostic errors" were found in the groups of hemispheral gliomas and of "central gliomas". The cerebellar astrocytomas and medulloblastomas showed in this respect the lowest incidence.

The case notes at the four Paediatric Clinics were reviewed in more detail and of the 69 patients with brain tumor it could be definitely established

that in five (7 per cent) the clinical picture had been misinterpreted and the diagnosis brain tumor delayed. The following tumors were finally diagnosed, teratoma localized to the left hemisphere, central glioma, suprasellar teratoid tumor, medulloblastoma of the fourth ventricle (newborn) and glioma of the optic nerve. In three of these cases encephalography was clearly indicated at a much earlier date and the diagnosis would then most likely have been established. The two other patients (one of them a 2 months old baby) had no distinct symptoms that could reasonably have arisen a suspicion of brain tumor. In none of these patients the delay of diagnosis influenced the outcome with the possible exception of the patient with glioma of the optical nerve.

Another approach to the problem to which extent a delay in diagnosis occur is to compare the group of patients with brain tumor referred as such to the Paediatric Clinic with the group of patients with brain tumor but referred with other diagnosis.

It was not possible to demonstrate a significant difference in the duration of the case histories between these two groups. The more important symptoms as headache, vomiting, papilloedema and other neurological signs showed about the same frequency in both groups and there was no evidence that any special type of tumor was more often represented among the patients referred with other diagnosis than brain tumor. The opposite could possibly have been expected as a significantly higher incidence of "diagnostic errors" were found among the hemispheral gliomas than among the cerebellar astrocytomas of the total series.

A significant difference could be demonstrated between the two groups regarding the age of the patients at admission. Of those referred with other diagnosis than brain tumor not less than 50 per cent were under 4 years of age against 15 per cent of those who came with the diagnosis brain tumor.

Table 4 shows that at least a part of the patients not referred as cases of brain tumor were admitted with a diagnosis definitely suggesting a neurological disorder requiring a more thorough examination. This is from a practical point of view very much the same as if the diagnosis cerebral tumor had been used.

During the period 1947–1956 a considerable number of patients without brain tumor were referred to the Paediatric Clinics in Stockholm with a suspicion of this diagnosis (Table 6). The number of such cases were almost as large as the number of cases with tumor indicating that when patients with neurological disorders of an uncertain nature appear the possibility of a brain tumor often is born in mind. The fact that so many of these patients were referred from other paediatric hospitals only shows that many difficult neurological cases require diagnostic resources not available in all country

hospitals. This is also in good accordance with the figures given in Table 5. The number of children with brain tumor referred to the Paediatric Clinics in Stockholm from children's hospitals in the country was as could be expected relatively low. Cases diagnosed as brain tumor are quite naturally sent directly to the neurosurgical clinics.

On the whole there seems to be little evidence that diagnostic errors, influencing the prognosis of brain tumors in the paediatric age group, occur to any large extent. There was admittedly in the total series a number of patients (about 20 per cent) who during their illness had other diagnosis than brain tumor. All of these cases can of course not be regarded as diagnostic errors. Mistakes no doubt occurred but it was not possible to arrive at an exact figure for the total series. Judging from the number of definite diagnostic errors registered in the four paediatric clinics it is likely that the figure is nearer 10 per cent than twenty. The figures compare favourably with the very few data found in the literature. In a series of 96 children with supratentorial tumors less than 50 per cent of the tumors were suspected prior to the child's hospitalization (Boldrey *et al.*). The corresponding figure for the present series may be estimated to about 70 per cent.

It is quite clear that in many cases who possibly might be regarded as diagnostic errors the outcome was not influenced by a delay in diagnosis. There was, however, in this group a relatively large number of patients (13 cases) with hemispheral gliomas and it cannot be excluded that at least some of these might have benefited by an earlier operation. Convulsions are common in this type of tumor and it must be emphasized that a rigorous examination including pneumoencephalography is necessary when children with "epilepsia" develop other neurological symptoms.

Electroencephalography is usually considered as a valuable adjunct to diagnosis and also to localization of the hemisphere tumors. Focal abnormalities and hemispheral asymmetries are electroencephalographic features commonly found in these tumors but are also seen in patients with convulsions of other origin. In the present series of patients (61 cases) without brain tumor but referred with this diagnosis 17 had epilepsia and of these 6 had focal abnormalities in their electroencephalograms. A diagnosis of hemisphere tumor can obviously not be made by electroencephalography but abnormal findings of the type described must be taken into account when pneumoencephalography is considered. In the supratentorial tumors of the midline structures and in the infratentorial tumors electroencephalography seems of little help. This was also the experience of the present investigation. Electroencephalograms of 24 patients with infratentorial tumors were studied and found to be normal or almost normal in about two thirds of the cases.

The number of otoneurological examinations and pneumoencephalographic studies performed in the Paediatric Clinics (23 and 18 respectively in 69 patients) may appear somewhat low. These low figures are, however, explained by the fact that in the majority of cases the history and clinical examination gave strong evidence of an intracranial expanding lesion and it was then for several reasons considered better to perform these investigations in the Neurosurgical Department. The diagnostic measures necessary for exact diagnosis and accurate localization of the lesion ought no doubt to be decided by the neurosurgeon.

Acknowledgement

We are indebted to H. Nordenstam, M.D., for helping us with the pathological classification of certain tumors.

Summary

During the ten-year period 1947–1956 293 children 15 years old or younger were treated for brain tumor at the hospitals in Stockholm. Of the verified tumors 80 per cent were gliomas and 54 per cent had an infratentorial and 46 per cent a supratentorial localization; 83 per cent were situated in midline structures.

The different types of tumor and incidence at different ages are shown in diagrams.

The most prominent symptoms, the duration of the histories and the results of treatment are briefly mentioned for each group of tumor.

About 20 per cent of the children had during their illness been treated with an other diagnosis than brain tumor. The highest incidence of such "possible diagnostic errors" were found in the groups of hemispheral gliomas and of "central gliomas". The possible implication of these figures is discussed.

The average annual incidence of brain tumors in the paediatric age group was found to be 0.036 per mille in Stockholm.

During the relevant period 69 patients with brain tumor had been admitted to the four Paediatric Clinics in Stockholm. These case records were reviewed in more detail. The main symptoms, diagnosis at admission and the results of certain diagnostic procedures are discussed. In five of these cases it could be established that the clinical symptoms had been misinterpreted and the diagnosis had been delayed. The outcome was not influenced by this except possibly in one case.

Patients referred to the Paediatric Clinics in Stockholm with a suspicion of brain tumor but later proved to have other neurological disorders, patients with brain tumor but referred with other diagnosis and patients with brain tumor referred with this diagnosis were compared and the results are discussed.

Aspects pédiatriques concernant des tumeurs cérébrales chez les nourrissons et les enfants.

Pendant 10 ans, de 1947 à 1956, 293 enfants âgés de 15 ans ou plus jeunes, étaient traités dans les hôpitaux de Stockholm pour une tumeur cérébrale. 88% des tumeurs vérifiées étaient des gliomes, 54% étaient localisées sous la tente du cervelet, et 46% au-dessus de la tente du cervelet; 83% étaient situés dans les structures de la ligne

médiane. Les différents types de la tumeur et l'indice à différents âges sont montrés par des diagrammes.

Les symptômes les plus prominents, la durée des antécédents et les résultats du traitement sont brièvement mentionnés pour chaque groupe de tumeurs. Environ 20% des enfants ont été traités durant leur maladie d'après un autre diagnostic que celui-ci posé pour une tumeur cérébrale. L'indice le plus élevé de telles « erreurs possibles de diagnostic » était trouvé dans les groupes de gliomes hémisphériques et de « gliomes centrales ». La conséquence possible de ces chiffres est discutée. On a trouvé qu'à Stockholm l'indice annuel moyen de tumeurs cérébrales dans le groupe comprenant l'âge pédiatrique était de 0,036 par mille. Pendant la période en question, 69 malades avec une tumeur cérébrale ont été admis dans les 4 cliniques de pédiatrie à Stockholm. Ces cas signalés étaient réexaminés de plus près. Les symptômes principaux, le diagnostic à l'admission et les résultats de certains procédés diagnostiques sont discutés. Dans 5 de ces cas, il a été établi que les symptômes cliniques ont été mal interprétés et le diagnostic a été remis. Le résultat n'était pas influencé par ceci, sauf dans un cas peut-être. Une comparaison est faite de malades renvoyés aux cliniques de pédiatrie de Stockholm, suspectés d'avoir une tumeur cérébrale mais chez qui on a constaté plus tard d'autres troubles neurologiques; de ceux avec une tumeur cérébrale, mais dont on a établi un autre diagnostic et de ceux dont on a établi ce diagnostic. Les résultats de cette comparaison sont discutés.

Pädiatrische Aspekte betr. Hirntumoren in früher Kindheit und Jugendalter.

Während einer 10-jährigen Periode, 1947–1956, wurden in den Hospitälern Stockholms 293 Kinder von 15 Jahren und jünger wegen Hirntumor behandelt. Von den verifizierten Tumoren waren 80% Gliome, 54% hatten eine infratentoriale und 46% eine supratentoriale Lokalisation; 83% lagen in der Mittellinie.

Die verschiedenen Typen der Tumoren und der Einfluss auf das unterschiedliche Alter der Kinder wurden in Diagrammen festgelegt.

Die am meisten hervortretenden Symptome, die Länge der Krankengeschichten sowie die Behandlungsresultate sind für jede Tumorgruppe kurz behandelt. Etwa 20% der Kinder waren während ihrer Erkrankung nicht mit der Diagnose Hirntumor, sondern einer anderen Diagnosestellung, behandelt worden. Der stärkste Einfluss solcher „möglichen Diagnoseirrtümer" machte sich in der Gruppe der Hemisphären-Gliome und der „Zentralgliome" bemerkbar. Die Möglichkeit der Einbeziehung dieser Formen wurde diskutiert.

In Stockholm betrug das Vorkommen von Hirntumoren im Kindesalter durchschnittlich per Jahr 0,036 pro Mille.

Während genannter Periode kamen 69 Patienten mit Hirntumor in den 4 Kinderkliniken Stockholms zur Aufnahme. Die Krankengeschichten dieser Fälle wurden eingehend beschrieben. Die Hauptsymptome, Einweisungs-Diagnose und die Resultate sicherer, diagnostischer Verfahren wurden diskutiert. Bei 5 dieser Fälle konnte festgestellt werden, dass die klinischen Symptome falsch ausgelegt und die Diagnose dadurch verzögert wurde. Das Ergebnis wurde dadurch nicht beeinflusst, ausser vielleicht in einem Falle.

Es wurden Patienten, die in die Kinderkliniken Stockholms eingewiesen wurden mit Verdacht auf Hirntumor, aber — wie sich später herausstellte — andere, neurologische Abweichungen aufwiesen, — Patienten mit Hirntumor, die aber eine andere Einweisungsdiagnose hatten und Patienten mit Hirntumor, die in der Tat mit dieser Diagnose aufgenommen wurden, verglichen und die erhaltenen Resultate diskutiert.

Aspectos pediáticos de los tumores cerebrales en la infancia.

Durante el decenio 1947–1956 fueron tratados por tumores cerebrales, en los hospitales de Estocolmo, 293 niños menores de 15 años. El 80 por ciento de los tumores estudiados eran gliomas; el 54 por ciento poseian una localización infratentorial, y el 46 por ciento supratentorial; en el 83 por ciento de los casos estaban localizados en estructuras correspondientes a la línea media.

Los diferentes tipos de tumores y su incidencia a las distintas edades se expresan mediante diagramas.

En cada grupo de tumores se mencionan brevemente los síntomas mas destacados, la duración de la historia y los resultados del tratamiento. Casi el 20 por ciento de los niños habian sido tratados en el curso de su proceso con un diagnóstico distinto al de tumor cerebral. La mayor incidencia de este "posible error diagnóstico" correspondió a los grupos de gliomas hemisféricos y "gliomas centrales".

En Estocolmo, la incidencia anual media de tumores cerebrales en la edad infantil fué de 0.036 por mil.

Durante el período adecuado fueron admitidos 69 pacientes afectos de tumor cerebral en las cuatro clínicas pediátricas de Estocolmo. Las historias de estos casos se revisaron con mayor detalle. Se discuten los sintomas principales, el diagnóstico en el momento de su ingreso y los resultados de determinados metodos de diagnóstico. En cinco de estos casos pudo ponerse de manifiesto que los síntomas clínicos habian sido interpretados erroneamente y con lo que se había demorado el diagnóstico. Ello no influenció su pronóstico, excepto en un caso.

Se estableció una comparación entre los pacientes ingresados en las clínicas pediátricas de Estocolmo con la sospecha de tumor cerebral, pero que más tarde se demostró que padecian otra alteración neurológica, los pacientes con tumor cerebral pero ingresados con otro diagnóstico, y los pacientes con tumor cerebral ingresados con el diagnóstico correcto, discutiéndose los resultados.

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Cerebral Palsy. A clinical study of 370 cases

by MARIT SKATVEDT

(Summary of Supplement 111)

The material is based on anamnestic information and on clinical examination of 370 children suffering from cerebral palsy. To illustrare the etiology of the disease, data are presented. The material shows a male predominance, 60 % against 40 % of females. A predominance of first-born children is statistically significant (52,7 %). Among the 370 patients familial occurrence on possible genetic basis was reported in siblings of two families. In two cases, cerebral malformations were demonstrated. There was no increase of maternal morbidity, nor was there information of possible external factors that might have caused injury to the fetus during pregnancy. Malformations known to be thus caused were not demonstrable in any case.

Information regarding the course of birth showed pathologic birth in 43.8 %, protracted birth and breech presentation being the most common forms. In 47 % of the children, information suggested perinatal asphyxia and/or symptoms of cerebral injury. In 26 children (7 %) the information pointed to kernicterus in the neonatal period.

Twenty-eight point two per cent of the patients were prematures (birth weight under 2500 g). As many as 49 % of the patients with bilateral spasticity were prematures, and of these a relatively large percentage had very low birth weight. Pathologic birth was less frequent among prematures than in the total number of cases (25 %). On the other hand, the material also shows a statistically significant increase in the number of large infants with birth weight over 4000 g. The percentage of normal birth weights (2500–4000 g) thus is considerably lower than in a normal population (55 % as against normally 80–85 %).

The material includes 25 pairs of twins. In 15 cases, the other twin was healthy, in 6 cases it was stillborn. In two pairs of twins both children had cerebral palsy.

Postnatal factors played a role in 18 cases (5 %); cerebral infection or other cerebral injury that might be the presumed cause of their cerebral palsy.

The etiological conclusions to be drawn from these data are discussed. They do not indicate an essential etiological importance of hereditary genetic factors or external fetal injuries in the organogenetic period to the development of cerebral palsy. But several conditions point to a dominant etiological importance of perinatal brain injuries. In a comparatively small group these cerebral injuries are due to kernicterus. It is pointed out that kernicterus is not rare in prematures without blood-group incompatibility, and the possibility is suggested that mild cases of kernicterus may occur, undiagnosed in the neonatal period, leading to cerebral palsy. Reference is made to animal experiments, autopsy findings, and clinical observations that point to deep-seated anoxemic cell lesions and hemorrhages in connection with birth as the main cause of cerebral palsy. The frequent occurrence of prematurity and clinical symptoms of asphyxia/cerebral hemorrhage in this study supports the view, but cannot be considered definite evidence. More significant is the greater number of pathologic deliveries and the demonstrated predominance of children with birth weight over 4000 g. It must be presumed that the same cerebral injuries which cause perinatal mortality, when of subletal degree are also responsible for cerebral palsy. The prophylaxis of cerebral palsy must be aimed at preventing these injuries. In about 5 % of the patients the disease probably was due to infective, anoxemic, or vascular injuries during infancy after the neonatal period.

The classification of the clinical types of cerebral palsy is described. The type division in the present study is the following: uncomplicated spasticity (56.7 %) with the subgroups of spastic hemiparesis (24 %) and spastic diplegia (32.6 %); uncomplicated athetosis (14.3 %); uncomplicated ataxia (6.5 %); the remaining 22.4 % of the patients, not referable to any of these types, but presenting a predominant mixture of pyramidal and extrapyramidal symptoms, were collected into a special group.

Pneumoencephalography (PEG) was made in 105 of the 370 patients. In 79 the examination permitted an evaluation of the ventricular system. Sixteen percent were found to be normal. Eighty-four percent showed pathologic dilatation of the ventricular system. Two types of pathologic findings were distinguished: those observed in spastic hemiparesis and those seen in all other types of cerebral palsy. In hemiparesis a pathologic finding was frequent (in 15 out of 16 cases). One patient showed normal ventricular system and atrophic changes of the cerebral surface. In the remaining 14 there was dilatation of the ventricular system. Assymetry of the ventricular system was a regular finding. In 11 cases the changes were bilateral, always with dilatation most marked contralateral to the hemiparesis. In three there was dilatation of the lateral ventricle only on the affected side. Nine

of the 14 patients had dilatation also of the third and fourth ventricle. Among all the other types of cerebral palsy, PEG was pathologic in 51 of 63 patients. Regardless of the clinical type, the pathologic findings were strikingly uniform, with mainly symmetrical dilatation of the lateral ventricles, and often dilatation also of the third (41 patients) and fourth ventricle (11 patients). The conditions of the sulci on the cerebral surface were estimable in 44 of the examined cases. The shape of the sulci was pathological in 35. The PEG findings seem to suggest that in cerebral palsy there is, besides other processes possibly a deep-seated central pathologic process, probably concerned with perinatal injury, which is presumed to be the most important cause of the disease. There is reason to believe that correlation exists between the degree of PEG changes and the degree of motor and mental defects in the patient. The PEG picture in cerebral palsy is strikingly like that seen in epilepsy without neurological symptoms.

It is suggested that organic epilepsy, cerebral palsy, and mental impairment due to cerebral lesions should be considered a pathologic entity, with the same etiology and the same pathologic-anatomical basis. Intelligence tests were attempted on 212 patients and the intelligence was found normal in 43.9 %, I.Q. between 85 and 50 in 21.7 %, and under 50 in 34.4 %. I.Q. was found the most reduced in the mixed group, the least reduced in athetosis.

Electroencephalographic (EEG) examination was made in 223 of the 370 patients. Eighty-eight (39.4 %) gave no pathologic finding. Thirty-seven (17 %) showed slight general dysrhytmia. In the remaining 98 patients (44 %) EEG was distinctly pathological. In the mixed group, clinically the most severe one, EEG was found normal in no less than half the number of those examined. Apart from these cases there was, on the whole, good correlation between the clinical findings and EEG. Thus, in hemiparesis, dysrhytmia usually was found contralateral to the paresis.

Eighty-two of the 370 patients (22 %) had a history of convulsions. Within the clinical types, convulsions were the most frequent in spastic hemiparesis (34.8 %), the least in ataxia and athetosis (12.5 % and 7.5 % resp.). Sixty-one of these 82 patients had EEG examination. Six showed normal EEG, and in nine it was pathological without epileptogenic foci; 46 had one or more epileptogenic foci. Epileptogenic foci (spike foci) also were found in 27 patients without manifest convulsive seizures. The location of the epileptogenic foci in the 73 patients were scattered over the whole of the brain, with slight predominance in central and temporal regions. A location in the posterior part of the brain, was predominant in the younger patients. Prematurity, pathologic birth, and symptoms of asphyxia/cerebral hemorrhage in the neonatal period occurred as often in those with convu-

sions as in the total number of cases. But among patients with epilepsy without cerebral palsy, these conditions were considerably less frequent than in those with cerebral palsy. On the other hand, in epilepsy alone, history of familial occurrence of convulsions is far more frequent than in the convulsion group of cerebral palsy. The I.Q. level, on an average, was considerably lower in the cerebral palsy patients with convulsions than in the cases in general. On the whole, epilepsy in cerebral palsy responds as favourably to anti-epileptic drug therapy as do epilepsy in general. In only four patients did the initiation of physical treatment appear to induce epileptic seizures.

Strabismus was demonstrated in 53 patients, and centrally conditioned reduction of vision in seven. Definite reduction of hearing was found in 19 patients, mostly in athetoids, in the form of high tone loss. Dysarthria occurred in 80 of 253 patients (31.5 %). It was the least frequent in patients with spastic hemiparesis, the most frequent in the athetoids.

The study includs six autopsies.

It is pointed out that althouth much may be achieved by physical treatment of cerebral palsy patients, the main task in combating the disease lies in the prevention.

Studies on Antihemophilic Globulin

by MARGARETA BLOMBÄCK

(Summary of Supplement 114)

The antihemophilic »globulin» (AHG) is the coagulation factor missing in hemophilia A. It is precipitated together with the plasma globulins, and is known to precipitate together with the fibrinogen in Fraction I of Cohn's Method 6 for plasma fractionation.

In the beginning of the present investigation, a method was elaborated, together with B. Blombäck, for preparing a stable fibrinogen from Cohn's Fraction I (bovine or human) by introducing glycine in optimal concentrations, in order to "salt out" the fibrinogen, and at the same time "salt in" the impurities into an aqueous glycine-ethanol-citrate mixture. The fibrinogen fraction coagulable with thrombin to about 88 per cent, was denoted as I-O.

Fraction I–O was found to contain most of the AHG present in normal plasma, as tested for its effect on the recalcification time in hemophilic A plasma. However, since the yield in Fraction I–O varied considerably, some details of the preparative technique were more thoroughly investigated.

Among them were the blood collection technique, the pH optimum for the stability of AHG, and the stability of AHG at different temperatures.

Fraction I–O in solution was used as starting material for further purification of AHG. It was then found possible to separate the AHG from the fibrinogen by precipitating the AHG-containing fraction at low ionic strength, in the presence of glycine and small amounts of ethanol. The fibrinogen could then be recovered from the supernatant. The yield of AHG was about 80 per cent of that in Fraction I–O. The AHG fraction still contained some fibrinogen. A purification of AHG of about 100 times that of plasma was obtained. The yield of fibrinogen in the fraction recovered from the supernatant was 70 per cent of that in Fraction I–O.

Clinical part (together with Dr. Inga Marie Nilsson, Allmänna Sjukhuset, Malmö): Since Fraction I–O was found to contain AHG, human Fraction I–O was administered to patients with AHG deficiency.

The first patient to whom Fraction I–O was administered was a girl with AHG deficiency (<5 per cent of normal) and prolonged bleeding time. Such patients have the clinical features of mild hemophilia, as well as bleedings from the mucous membranes. Fraction I–O was given; not only did the AHG level rise accordingly, but the bleeding time was also normalized.

Under cover of Fraction I–O, hysterectomy (necessited by the patient's severe menstruations and sensitization to blood) was performed. Other patients with the same hemorrhagic disorder were traced. The effect of Fraction I–O was the same as in the first patient. The effect on the bleeding time could still be demonstrated when the AHG had been removed by filtration. This implied that the prolonged bleeding time could be normalized by a factor, not identical with AHG, present in normal human plasma. Purified fibrinogen proved to have no effect on the AHG level or bleeding time. When Fraction I–O was prepared from hemophilia A blood, the prolonged bleeding time of the above patients was normalized by this fraction. This indicated that hemophilia A patients (who have a normal bleeding time) have normal amounts of the factor correcting the bleeding time.

In the meantime, the families of these patients were investigated (together with Dr. I. M. Nilsson and Dr. I. von Francken). A significantly low AHG level was found in one of the parents in each family. Low AHG levels were also recorded in several of the siblings of the parents in question, equally distributed between males and females. Subjects low in AHG had children with both normal and abnormal AHG values. In the affected persons, the AHG level ranged from 2 to 62 per cent of normal; those with hemorrhagic symptoms had values of less than 20 per cent of normal. The gene causing the AHG deficiency was considered to be autosomal, dominant with varying expressivity.

Since this hemorrhagic syndrome clinically resembled von Willebrand's disease known from the Åland Islands, the investigation was continued there (together with Dr. I. M. Nilsson, E. Jorpes, B. Blombäck and S.-A. Johansson). The patients were placed at our disposal by R. Jürgens and his co-workers. They, as well as the authors, noted decreased AHG in these patients, in addition to the prolonged bleeding time. Jürgens, however, also found a deficiency of Platelet Factor 3, which was not found by us. The response to human Fraction I–O was the same as in the patients described above, *i.e.* the AHG level rose according to the activity of the preparation, and the bleeding time was normalized.

Twelve hemophilia A (AHG <1–2.5 per cent) patients were treated in connection with acute bleedings, such as gastrointestinal bleedings and joint bleedings, and in connection with operations such as appendectomy and tooth extractions. By increasing the AHG level to 40–80 per cent of normal, and by maintaining it at 20–30 per cent, the necessary surgical operations could be performed, and healing completed without abnormal bleeding. When any local or general infection was present, the AHG consumption was observed to be more rapid than usual. At the time of writing, one patient has received the fraction 33 times. No side reactions and no antibody production have been observed.

On the Cerebrospinal Fluid in Normal Children and in Patients with Acute Abacterial Meningo-Encephalitis

by STEN WIDELL

(Summary of Supplement 115)

In an investigation of the cell content, total protein content and the electrophoretic pattern of 123 samples of cerebrospinal fluid (CSF) from 98 normal children, aged 0–13 years, the following observations were made.

The cell content of the CSF was higher during the first 3 months of life than later in childhood. The range of variation of the individual values was considerable, above all during the first weeks of life. The total protein content of the CSF was also larger during the neonatal period than during the rest of childhood. During the first year of life the mean protein content decreased successively, reached a minimum between the ages of 9 months and 2 years, then began to increase again and continued to do so throughout the rest of childhood.

Of the electrophoretically separated protein fractions of the CSF, albumin

in its variation with age showed a distinct parallelism with the total protein content. The mean albumin concentration in the CSF, expressed in per cent of total protein, was thus highest during the neonatal period and lowest in children 9 months to 2 years of age, after which it again successively increased. The other protein franctions of the CSF, except gamma-globulin, showed roughly the converse variation.

During the first week of life the relative concentration of albumin in the CSF was higher than in the serum. The physiologic basis of this is presumably mechanical irritation of the meninges in association with delivery and subsequent increase of passage of serum protein into the CSF space, especially of the relatively small dispersed albumin molecules. The variations in the amount and composition of the CSF protein in different ages probably depend on variations in the relative amount of the admixture of serum protein during passage of the CSF from the ventricles to the lumbar subarachnoidal space. The increased addition of serum below 9 months of age is probably due to an increased permeability of the blood-CSF barrier. The changes occurring after 2 years are probably related to a relatively decreasing function of the choroidal plexus with increasing age.

Investigations of the CSF from 31 adults showed a continued increase in the total protein content and the relative albumin concentration of the CSF as well as a continued decrease in the relative concentrations of beta-globulin and X-fraction. These observations suggest a further relative decrease in the CSF production by the choroidal plexus.

Analyses of 256 CSF samples from 119 patients, including 60 children, with acute abacterial meningo-encephalitis revealed as follows.

At the time on onset of the disease the cell content of the CSF was usually higher in mumps meningo-encephalitis than in meningo-encephalitis of other origin. While no relationship was found between the CSF changes and the clinical picture during the acute stages of mumps meningo-encephalitis, a clear correlation was demonstrable in meningo-encephalitis of other origin between the clinical symptoms at onset and the cell and protein content of the CSF. During the later course of the disease most patients with mumps meningo-encephalitis were symptom-free. In meningo-encephalitis not related to mumps, however, persistent symptoms in the form of tiredness, headache, dizziness, loss of memory, concentration difficulties, irritability, abnormal intolerance of light and sound were more frequent and to a larger extent accompanied by pronounced changes in the CSF: marked increase in the cell content, protein content and the relative concentration of gamma-globulin.

Of the electrophoretically separated protein fractions of the CSF, the albumin during the initial stage of the disease was markedly increased, the

relative concentration exceeding that in serum, at the same time as the other protein fractions of the CSF were below normal. During the further course the pattern gradually became normal although the relative gamma-globulin concentration was above normal for some time afterwards, especially in patients with severe symptoms. The increase in the gamma-globulin concentration occasionally persisted for more than 3 months.

Judging from the results obtained, the changes in the central nervous system in mumps meningo-encephalitis are probably relatively benign and localized mainly to the meninges. The other meningo-encephalitides represented a heterogenous group with respect to the etiology, severity and duration of the disease and probably also regarding its pathologic-anatomic localisation. In addition to the etiology of the disease, the clinical picture was probably dependent on variations in the individual mode of reaction. Thus, in the series examined an increase was noted in the frequency of clinical symptoms and pathologic CSF findings with age.

The abnormalities in the electrophoretic pattern of the CSF protein are probably due to disturbed meningeal permeability. During the initial stage of the disease serum albumin will pass into CSF space more readily than the remaining serum protein fractions. The increase in the relative concentration of gamma-globulin during the later course of the disease might partly be ascribable to a relative retardation of the reabsorption to the blood stream. However, in cases with a pronounced increase of the gamma-globulin the possibility of a cerebral or meningeal site of production must be considered.

No correlation was found between the electro-encephalographic findings and the changes of the CSF in the series.

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The Danish Pædiatric Society

Meeting March 26, 1958

CASE REPORTS: T. SAMSØE-JENSEN: Eczema herpeticum Kaposii.—KELD NIELSEN: A case for diagnosis.—B. ZACHAU-CHRISTIANSEN: Osteogenesis imperfecta.—J. D. LITTAUER: Winckel's Disease.

T. Samsøe-Jensen and B. Zachau-Christiansen: Complications of Prophylactic Tetanus Antitoxin (TAT) Inoculation.

In the prophylactic inoculation for tetanus intramuscular injections of highly purified horse or ox serum are employed. On account of the numerous injections which are administered the question of the incidence of complications is of great practical significance in the treatment of casualities, particularly as this inoculation procedure must continue, as far from all of the population are effectively immunized against tetanus. The purification and concentration of the antitoxin-containing sera have reduced the incidence of serum sickness from 40–60 per cent to 5 per cent while the incidence of immediate reactions (conditions of shock, acute allergic reactions) does not appear to be influenced (*Laurent & Parish*, 1952). From Denmark, it has been recorded by *Scheibel* (1953) that after approximately 400,000 injections of TAT during the period 1943–1953, 6 fatal cases of shock occurred.

The authors' personal investigations are based upon 14,702 casualities cases treated in the Casuality Department, Sundby Hospital, Copenhagen, during the period 1.X.1955 till 30.IX.1956. In 1,656 cases prophylaxis for tetanus was indicated but was omitted in 313 cases for various reasons (adequate immunization, recent administration of TAT, side-effects occurring after a previous injection of TAT, positive skin reaction to horse serum, manifest allergic disease, unaccompanied children, drunkenness). TAT was administered to a total of 1,343 patients. One year after treatment, by means of a detailed questionnaire or personal interview, the authors were able to contact 1,273 of the patients, i.e. the percentage of answers was 95. Out of the patients followed up in this manner, only 64 or 5 per cent had experienced side-effects. Characteristic serum sickness occurred in 20 (1.6 per cent). In the majority, the sickness disappeared within 10 days but 2 patients stated that they had experienced prolonged discomfort following the injection of serum. One of these, a boy aged 11 years, suffered from recurrent painful swelling of the joints for several months. He had also experienced swelling of the knees following administration of TAT two years previously. As the only symptom, 8 patients experienced unilateral enlargement of the lymphatic glands in the inguinal region. Local reaction at the site of injection was stated to have occurred in 23 patients and this took the form of localized urticaria in 2 patients. In 11 patients uncharacteristic systemic symptoms such as headache,

vertigo, pyrexia and malaise were present. In two cases, both boys, immediate reactions in the form of collapse and convulsions occurred. Both of these patients recovered spontaneously in the course of a few minutes. More frequent incidence of side-effects in children could not be demonstrated. Out of the 64 patients in whom side-effects occurred, 27 had received TAT previously but neither of the two patients who developed immediate reactions had received antitoxin injection previously. Out of the remaining 1,209 patients in whom side-effects did not occur, 457 stated that they had received TAT previously from 1 to 7 times. One patient with side-effects (Quincke's oedema and urticaria) had received TAT and penicillin. This patient was known to be allergic to penicillin and was therefore excluded from the material.

Conclusion: When certain precautions are observed, the incidence of side-effects following prophylactic inoculation for tetanus is relatively slight and the severity of the symptoms recorded is not particularly pronounced.

Discussion:—*E. Thamdrup.* In the Children's Hospital, Fuglebakken, Copenhagen, a girl aged 11 years was admitted this year who had suffered from periodic painful swelling of the joints. The illness commenced three weeks after an injection of TAT (ox-serum). The temperature and BSR were normal during the entire illness. The AST and ASH reactions were only doubtfully raised and the SAT reaction was normal. There had not been any preliminary infection of the throat. There is no proof that the TAT injection caused the joint condition in this patient but it was a striking observation that the temperature and BSR were normal throughout the entire illness.

Other participants in the discussion raised the question of the protective effect of diphtheria-tetanus prophylactic vaccine. The two first injections which are administered with an interval of a month must not be considered to give adequate protection. Adequate protection is not achieved until after the third injection. Whether a casuality case who has received all three injections should receive both a booster dose and tetanus antitoxin, has not yet been elucidated and, therefore, the latter procedure should probably be elected.

B. Zachau-Christiansen: **The Insulin Requirement in Childhood.**

This subject is closely related to the problem of growth in diabetic children. Such children are, as a rule, stated to present retardation in growth, although this retardation appears to be caused by the occurrence of the so-called diabetic dwarves, the incidence of which is given by figures varying from 25 to 5 per cent. It has, however, been stated that the growth of diabetic children may be normalized by adequate diet and insulin administration and thus normal physical development indicates adequate dosage. Only a few authors have calculated the relative dosage of insulin and this has been found to be around one unit per kg body-weight during the entire period of childhood. A series of 80 cases of juvenile diabetes mellitus from two paediatric departments in Copenhagen is presented. An account is given of the age at the commencement of the disease and of the growth. Until puberty normal weight was found and possibly some retardation in growth in height. At puberty, retardation of growth, most marked where girls are concerned, was observed. This may have been caused by the rather considerable degree of glucosuria permitted. By means of an analysis of variants, it was demonstrated that the relative insulin requirement, irrespective of sex, age, duration of the disease and apparently irrespective of the type of insulin employed, is constant. The mean figure and the scatter is 1.1 ± 0.4 international units per kg. The absolute insulin requirement follows the weight curve graphically.

DISCUSSION.—*O. Steinicke* put the following questions: 1. In calculating the insulin requirement, was the state of adjustment of the children taken into consideration? Some children examined have a very high daily excretion of sugar and their insulin requirement is, therefore, not exactly what it ought to be. 2. Do the insulin requirements calculated in units per kg hold true also for children who are overweight or should the requirement be calculated from the normal weight for the height of the child? 3. Is the insulin requirement calculated in the same manner whether a rapidly acting insulin or insulin with a slower action is administered and is there a difference in the requirement if one or two injections are administered daily?—*Agnete Bræstrup* did not consider that a simple calculation of the dose of insulin per kg body weight gives information concerning the insulin requirement in children. The endogenic production of insulin may be inhibited by administration of increasing doses of insulin and a constant daily dosage of insulin may thus conceivably have originated as a sequel of overdosage. One of the causes of overdosage of insulin is that insulin symptoms are seldom recognized as the slow acting insulin preparations only occasionally give rise to alarming symptoms. If this condition is borne in mind such symptoms may, however, be observed in the majority of diabetic children. Many of the children become quiet and sleepy, others become difficult and irritable, some develop paraesthesia, predominantly in the arms and legs, and difficulty in determining distances with micropsia is also frequent. Some of the overdosed children suffer from adiposity which is cured by a diet corresponding to their age and a dosage of insulin corresponding to this. Many children suffer from hepatomegaly which disappears on reduction of the dose of insulin. It would be of significance if the criteria for estimating the insulin requirement in a child could be revised. Theoretically, normal blood sugar variations and excretion of 10–20 g sugar per 24 hours is the uncontested goal of treatment but in the efforts to attain this, clinical symptoms must not be ignored which can give information concerning failure of the physiological mechanism as a sequel of overdosage.—*F. Tudvad:* Our material and the mean values found must by no means be regarded as optimal. We are, however, of the opinion that the material in the form presented shows that, on an average, the diabetic children have been given too much to eat and consequently too much insulin.—*B. Zachau-Christiansen* does not consider that administration of insulin alone nearly completely inhibits the endogenic production of insulin in childhood. In adults in whom probably inhibition has been studied only, very considerable endogenic insulin formation persists as can be revealed by autopsy findings. The investigation has been simplified; the authors are aware of the many individual differences but hesitate to make deductions from a heterogenous material such as that employed. The differences are indicated, however, by the large scatter. Knowledge of the constancy of the relative insulin requirement and to the extent of its mean value must, however, be of a certain importance in comparisons. The figures here are regarded as too large.

T. Samsøe-Jensen and K. Hauge Kristensen: **Some Investigations Concerning the Binding in Vitro of Skin Sensitizing Antibodies to Skin Cells and Other Tissues.**

The authors' introductory experiments were made with the object of investigating whether the antibodies of the skin (grass pollen reagins) could become bound in vitro to skin, muscle fascia and peritoneal connective tissue. The skin was obtained as skin-grafts, divided, rinsed in normal saline and employed 1. fresh and untreated, 2. after freezing in an acetone-carbon dioxide snow mixture and 3. after heating for ½ hour to 60°C. In some experiments 4. fresh skin from areas treated with hyaluronidase

was employed. Muscle fascia and peritoneal connective tissue were employed fresh and untreated. Four drops of antibody-containing serum were added to the test tubes containing the tissue fragments. The test tubes were allowed to stand for 24 hours in a refrigerator (binding) and then passive transference to a series of volunteers was conducted with the supernatant fluid and with the control serum from a test tube without tissue fragments. The size (in area) of the Prausnitz-Küstner reaction (P.K.) was employed as expression of possible binding. Definite weakening of P.K. reactions was demonstrated with serum influenced by fresh skin (15 tests), by cold-treated skin (10 tests) and by hyaluronidase-treated skin (7 tests). No weakening of the skin reactions was observed with serum influenced by warmed skin (8 tests), muscle fascia (12 tests) and peritoneal connective tissue (5 tests). The conclusion is drawn that a binding of the skin sensitizing antibodies to the skin occurs in vitro. Warming of the skin denaturizes the proteins and destroys the binding ability. Not all mesenchymal cells are able to bind skin sensitizing antibodies.

B. Zachau-Christiansen, O. Steinicke and E. Thamdrup: **Treatment of Dyspepsia with Sterosan.**

Sterosan (Geigy), 1-methyl-5,7-dichlor-8-oxychinolin, was administered for 10 days to 62 children suffering from dyspepsia and admitted to the Paediatric Department, Sundby Hospital, and the Children's Hospital, Fuglebakken, Copenhagen, on even dates. The preparation was not administered to 73 children admitted on odd dates. Dietary treatment was identical in both groups. Sterosan was administered orally in the following doses: 30 mg × 4 to children under the age of one year, 50 mg × 4 to children between the ages of one and three years and 60 mg × 4 to children over the age of 3 years. No difference between the groups could be elicitated by the following investigations: 1. The average number of stools on the 3rd, 5th, 10th, and 15th days, 2. the number of children with normal stools on the 5th, 10th and 15th days, 3. the time at which the children attained an adequate diet, 4. the time when definite increase in weight occurred, 5. the incidence of recurrences. No side-effects due to the preparation were observed.

F. Tudvad: **The Value of Follow-up Control of Premature Infants.**

The case histories of all premature infants admitted to the Children's Hospital, Fuglebakken, Copenhagen, in 1951–54 were reviewed. These totalled 287 and of these, 30 or 10.4 per cent had died. Premature infants were discharged when a weight of 3,000 g had been attained. For the group with birth weights of 1,001–1,500 g this was achieved, on an average, at about the age of 90 days, in the group 1,501–2,500 g about the age of 70 days and in the group 2,001–2,500 g about the age of 50 days. Follow-up control examination was offered to all the premature infants on discharge but only 55 per cent reported thrice or more frequently. One quarter of those who did not report were illegitimate as compared with 1/12 of those who reported. Among the 113 children who reported thrice or more for control, no abnormalities were found in 52 per cent. Craniotabes was demonstrated in 25, anaemia (Hb under 75 per cent) in 11, gastro-intestinal disease in 9, skin diseases in 7, throat and respiratory disease in 6, mental retardation in 5, muscular weakness in 4, strabismus in 3 while one case of each of the following conditions was encountered: cerebral paresis, abscess resulting from BCG vaccination, funnel chest, congenital dislocation of the hip and hernia requiring operation. On control examination, the haemoglobin percentage was deter-

mined and the red cells counted. Average values for these figures for the children followed-up until the age of one year were found which corresponded entirely to the figures found by *Rothe-Meyer & Kreutzfeldt* in 1953. The premature infants in the work quoted received 250 mg iron daily until the age of one year while the premature infants in the present material received only 50 mg iron thrice daily until they were able to take one full meal of purée at about the age of 5 months. Finally, it was found that 45 per cent of the premature infants in the group with birth weight of 1,001–1,500 g, 60 per cent of the group with birth weight of 1,501–2,000 g and 78 per cent of the group with birth weight of 2,001–2,500 g had attained the average weight for full-time infants minus 10 per cent by the age of one year.

DISCUSSION:—The length of the period of hospitalization of premature infants was discussed and it was unanimously decided that these children can, as a rule, be discharged when they have attained a weight of 2,500 g.

Meeting, April 23, 1958

***S. von Rosen*, Early Diagnosis and Early Treatment of Congenital Dislocation of the Hip.**

For a great number of years, all the children born in the Maternity Department of The General Hospital in Malmö have been examined routinely by a paediatrician during the first days of life. Since 1952, this routine examination has also included examination of the hip joints for the presence of the Ortolani click. Since during the same period, more than 99.5 per cent of all deliveries in the City of Malmö take place in the Maternity Department, this implies that practically all the newly born infants are examined in this manner. During the period, 1952–1955, 11,995 infants were born. The newborns who exhibited clicking in the hip joints were remitted to the Orthopaedic Department for evaluation and treatment. A review and account of the first 8 cases (with 14 clicking hips) were published in Acta Ortop. Scand. Volume 26 No 2. It was there stated that in all cases the clicking observed corresponded to an actual reduction of the dislocation. X-ray examination showed an upward displacement of the femur which could scarcely be due to anything but a dislocation of the hip, even although the X-ray films could not be termed 100 per cent reliable. The children involved were treated with an abduction pillow or abduction plate of various types. In only two of the cases was admission to the Orthopaedic Department for treatment in plaster required. The remaining cases were treated as out-patients. In all cases, treatment was completed and the children commenced walking at about the age of one year. Follow-up X-ray examination showed normal or nearly normal development of the hip joints. Since then, 6 further cases have been diagnosed and treated. In the treatment a new type of fixation splint developed in the Orthopaedic Clinic was employed and proved suitable. The results obtained were good in all respects. The number of cases diagnosed is in accordance with the incidence of congenital dislocations of the hip previously encountered in the City and since the introduction of this method of early diagnosis not a single case of dislocation of the hip has been discovered at a later period. This is strong evidence that the cases have neither been over- nor under-diagnosed. During the past year a method of X-ray examination has been elaborated which appears to be 100 per cent reliable concerning both the establishing of the diagnosis and the control examinations (Acta Radiologica, Volume 49, No. 2). Recent experience also appears to indicate that a considerably briefer period of fixation than

that previously employed suffices to produce correct development of the hip joint. The diagnosis and treatment of congenital dislocation of the hip already during the first week of life appears to be so valuable and so much superior to the previous practice that in the examination of newly born infants in maternity departments by paediatricians the hip joints should also be included. The treatment should be guided and supervised by an orthopaedic surgeon who has the best possibilities of following and evaluating the course of treatment and its results.

Discussion:—*C. Friderichsen:* Can the Ortolani click still be elicitated at the age of 5 weeks? At this age approximately 2,500 infants are examined annually in the Child Welfare Centres in Copenhagen, i.e. if the incidence is 1.6‰, 4 cases of congenital dislocation of the hip should be demonstrated annually. Dr. von Rosen's paper demonstrates the significance of paediatric inspection of all newly born infants.—*A. Berthelsen:* The treated cases of congenital dislocation of the hip often develop arthrosis at the age of 20–40 years while the untreated cases do not develop arthrosis. There is no proof that early reposition ensures that the patients will not develop arthrosis. Dr. Berthelsen was of the opinion that health visitors should be taught to investigate the hip joints as the majority of children with congenital dislocation of the hip are detected by the health visitors, as a rule, before the children attain the age of one year. Only a few children are born with dislocation or predislocation. Dysplasia of the acetabulum is present at birth and dislocation does not occur until the age of 4–5 months. It has been suggested, therefore, that the name of the condition be changed to congenital dysplasia of the hip.—*Hj. Larsen* was of the opinion that it is important that the condition be recognized and treated as early as possible. Whether the prognosis is improved in this case is not yet known but the musculature becomes inadequate if the dislocation is not reduced. Midwives should be able to diagnose these diseases.—*P. Plum* was convinced that it is important to find and treat these conditions as soon as possible. Children suffering from cerebral palsy who lie on one side may develop dislocation in the other hip.—*A. Rothe-Meyer:* How late may "clicking" be found in the hip and how late may von Rosen's treatment be instituted? Is the Ortolani click present in cases of subluxation?—*Hj. Larsen:* In Finland children with congenital dislocation of the hip are not treated until the age of 4–5 years and they are more difficult to treat at this age.—*P. W. Bræstrup* does not consider arthrography advisable. Exposure of the hip joints to radiation may be dangerous particularly in girls.—*von Rosen:* The diagnosis should be established in the first week of life as the musculature develops markedly during the first month and reposition at the age of 4–5 weeks is more difficult and it is more difficult to maintain reduction. The majority of the changes in the head of the femur and the acetabulum are secondary. It is possible that cases of subluxation are not discovered but the number of cases found in Malmö correspond to the previous incidence and no cases of congenital dislocation other than those found in the first week of life have been encountered. Employing the methods of X-ray examination mentioned the subluxations may perhaps be demonstrated. X-ray examination reveals that the acetabulum and head of the femur develop normally in the cases treated early. How often does this occur in the cases in which treatment is commenced late? Arthrography should not be employed as a routine.

Henning Andersen: **Marfan's Syndrome.**

Recent investigations have demonstrated that the most important *cardio-vascular* symptoms in Marfan's syndrome are not septal defects nor aortic stenosis as previously

presumed but ectasia of the aorta and pulmonary artery on account of abiotrophy of the media in these vessels. The changes in these vessels may become so pronounced that dissecting aneurysm and spontaneous rupture occur. Changes in the media of the large vessels indicate a pathological condition in the elastic fibres as the primary defect of the disease and this may also explain the weakness and laxity of the supportive system. The common factor in the suspensory apparatus of the lens and the media of the aorta is not yet elucidated but this is possibly the crux of the matter. Similarly, it has not yet been explained how a defect of the elastic fibres may upset the equilibrium of the form regulation of the bones. The basic defect in the disease has not yet been demonstrated. Recent experiments with rats, which when fed with seeds of lathyrus odoratus, develop kypho-scoliosis, hernias and dissecting aneurysm of the aorta, viz. symptoms which greatly resemble but are not entirely identical with those found in Marfan's syndrome may be of assistance in solving the problem. The active substance in these experiments appears to be an amino proprionitril and in these intoxications great quantities of mucopolysaccharides in the tissues occur as also in the aortic defects on Marfan's syndrome. The treatment has, hitherto, been symptomatic, orthopaedic, paediatric, ophthalmological, thoracic surgery etc. It is of great prophylactic significance that the other members of the family are investigated in close co-operation with geneticists. Two boys aged about 14 years with typical Marfan's syndrome were demonstrated. One of these had changes in the hip and spine resembling osteochondrodystrophy. The other patient had previously been regarded as an atypical case of progressive muscular dystrophy on account of muscular weakness.

Discussion.—*A. Berthelsen:* Only 20–25 per cent of the various forms of embryopathy are hereditary. A number of defects may now be produced experimentally, e.g. epiphysioloysis. Growth of an epiphysis may be arrested operatively.—*T. Iversen* mentioned a case of Ehlers-Danlos syndrome and osteogenesis imperfecta demonstrated previously and regarded as a profound mesodermal malformation.—*P. Plum:* Can the diagnosis be established when there are neither ocular nor cardiac changes? Has previously arrested the growth in a few tall children with Sexadien treatment (Dienoestrol).—*Henning Andersen:* The disease is a hereditary dominant but 70–30 per cent of the cases develop spontaneously. The diagnosis cannot be established solely from the symptom of long extremities but ocular changes, preferably dislocation of the lens, must also be present. In some "Marfan families" rupture of the aorta or dislocation of the lens may be present without long extremities. Dr. Andersen has attempted to inhibit growth in a boy by means of cortisone in moderate doses. In this manner, maturation of the bones is not inhibited.

Meeting, May 18, 1958

✓ *Thomas Otte Iversen:* **Idiopathic Hypoproteinaemia.**

A case of idiopathic hypoproteinaemia occurring in a boy aged 9 months is presented who had shown a tendency to oedema from birth. During hospitalization, persistent serum protein levels of about 3–4 per cent were found; the quantity of albumin comprizing approximately 45 per cent. In addition, there was pronounced hypocalcaemia, relative lymphocytopenia and daily frequent loose watery stools. On the other hand, the urine contained no albumen and the renal and hepatic functions were normal. During the entire period of hospitalization, the condition was dominated by frequent, often prolonged, attacks of tetany, progressive loss of weight and, on the whole,

steady deterioration of the general condition. Despite protein-rich, salt-poor diet with supplementary calcium both orally and parenterally, human albumin intra-tibially and blood transfusions, death occurred approximately 10 weeks after admission. Autopsy revealed that the pancreas, supra-renal glands, parathyroid glands, intestinal mucosa and lungs were normal. There was insignificant periportal connective tissue proliferation in the liver. The case was compared with similar cases in the literature and it was confirmed that oedema, hypo-albuminaemia, hypocalcaemia, lymphocytopenia and diarrhoea are the symptoms which occur most frequently and they undoubtedly form a nosological entity which cannot be explained solely by the only constantly occurring symptom, viz, hypo-albuminaemia. The pathogenic possibilities are discussed. Primary resorption defects and sub-clinical liver disease appear to be less probable. Reduced and/or abnormal protein synthesis is considered to be the central feature in the pathogenesis of the disease.

Karen Damgaard and J. Flamand Christensen: **Erythroblastosis Foetalis.**

A review of the results of treatment of the live-born infants with erythroblastosis foetalis treated in the Department of Paediatrics and Maternity Department, Odense, during the period 1947–57 revealed a total of 74 cases of which 3 were due to anti-A-influence. Exchange transfusion treatment was introduced in 1950. Prior to that time 10 infants were treated and of these one died shortly after birth, 5 had symptoms of kernicterus and 4 of these died. Four of these children are healthy. After 1950, 42 children with erythroblastosis foetalis were born in the Maternity Department and of these 18 received exchange transfusion. Six of the children died, two on account of hydrops foetalis and anaemia immediately after birth, one on account of intracranial haemorrhage, one from asphyxia and complete atelectasis, one from kernicterus and one from intraperitoneal haemorrhage on account of a vascular lesion following transfusion. The remaining 36 children have all been followed-up and none have cerebral sequelae. Twenty-two children were admitted a shorter or longer time after birth and 10 of these received exchange transfusion. Four or possibly 5 children developed cerebral palsy. Out of these children, 13 were healthy on follow-up examination. The investigation demonstrates the significance of the recognition of rhesus-immunization during pregnancy so the mother can be admitted for delivery in a Maternity Department. Cases which are not due to rhesus-immunization will not be recognized until after birth and, therefore, the necessity of immediate admission of all cases of jaundice occurring during the first day for investigation and possible therapy is emphasized.

Karen Damgaard: **Spontaneous Infantile Chylothorax.**

A male infant aged 8 days was admitted with spontaneous right-sided chylothorax. Symptoms had been present from the 5th day of life. At the age of 2½ months, chylous ascites developed. A total of 44 pleural aspirations and 14 abdominal paracenteses were undertaken and a total of approximately 10 litres of chylous fluid withdrawn. The child did not thrive, was weak and tired and died at the age of 5½ months. Administration of vitamin A revealed that the child absorbed the aqueous solution of the vitamin best and that this was excreted in the chyle. At autopsy, small cysts were found on the peritoneal surface of the intestine. These proved to be distended lymph channels. The lymphatic glands were slightly enlarged and succulent. Microscopic examination revealed greater or lesser dilatation of the sinuses in the lymph

glands and of the lymph channels in the surrounding tissue. The thoracic duct and the cisterna chyli could not be found. Microscopic examination of lymph-containing tissue at the usual site of the thoracic duct revealed a space lined with epithelium but this was too thin-walled to be the thoracic duct. The conclusion is drawn, that the chylothorax and chyloascites were probably due to congenital deformities of the lymph vessel system with obstruction of the flow of lymph.

Discussion.—*J. Vesterdal:* In cases of chylous ascites the differential diagnostic possibilities must be considered and this is illustrated by the following case: A boy aged 8 years, recently admitted to the Department of Paediatrics of the University Hospital, had ascites of varying degrees for several years. Paracentesis of the abdomen revealed chylousresembling fluid. Explorative laparotomy revealed, however, that a reduplication of the intestine in the form of a soft thin-walled cyst approximately the size of a football was present. This had been punctured in the paracentesis and chylous ascites was thus not concerned.

Steffen Hvidt: **Two Cases of Turner's Syndrome.**

One of the patients was a girl aged 14 years and showed the following anomalies: Retarded growth in height, increased distance between the areolae of the breasts, webbed neck, deformed ears, low hair margin, loose skin and habitual dislocations, hypoplasia of the maxilla and mandible, high palate, epicanthus, impaired hearing, coarctation of the aorta and an I.Q. of 88 per cent. The excretion of gonadotrophic hormone was increased while the excretion of oestrogenic hormone and 17-ketosteroids were about the lower limit of normal. The other patient was a girl aged 9 years. During the first months of life the extremities were swollen. The bodily conformation is now plump. The bridge of the nose is broad and the palate high. Coarctation of the aorta is present. The I.Q. is 76 per cent. In both patients skin biopsy revealed masculine chromosome composition. The difficulty of establishing the diagnosis prior to puberty when the hormone analyses reveal normal conditions is stressed. After puberty primary amenorrhoea may be the only symptom. Sex-determination by examination of specimens from the skin biopsy, leucocytes, scrapings from buccal or vaginal mucosa are decisive for the diagnosis in doubtful cases.

Discussion.—*J. Vesterdal:* Has the chromatin in leucocytes and the epithelial cells in the urine been investigated?

Meeting, June 17, 1958

Steffen Hvidt: **Polymyositis of a Type Resembling Muscular Dystrophy.**

Two un-related boys aged 9 and 6 years were demonstrated. In each boy the diagnosis of polymyositis had been verified by two muscle biopsies. Both of the children commenced walking late, walked with a rocking gait and stood up employing the same technique as do patients with muscular dystrophy; they presented pseudohypertrophy of the leg muscles. Factors not typical for muscular dystrophy were the absence of familial predisposition, the fact that the condition had been stationary from approximately the 3rd.–4th. years of life and the observation that the nuchal muscles were markedly involved. The development of the disease had not been associated with acute episodes and intra-uterine development cannot be excluded. One of the patients had, late in the course of the disease, slight stiffness, pain and tenderness of the muscles of the extremities. Both patients had I.Q.s of 82 per cent and had at various times

lived in the same flat. X-ray examination of the skull, cerebro-spinal fluid, neurological examination and electroencephalography were normal. A series of diseases with a similar histological picture, including the "collagen diseases", could be excluded. The serum transaminase (GO–T) was considerably raised in both of the patients while the spinal transaminase was normal. The excretion of creatinin in the urine was reduced. Electromyography revealed myogenic disease. One of the patients was treated with 12.5 mg prednisone daily for one year with some clinical improvement while the other patient received prednisone 12.5 mg daily for two months without any clinical effect. In both cases the histological picture showed considerable clinical improvement. It was concluded that muscle biopsy should be undertaken in all cases of supposed progressive muscular dystrophy where there are atypical features.

Discussion.—*Fuglsang-Frederiksen:* Is this form of polymyositis of the same nature as others? Why was the I.Q. low? This is not a feature of polymyositis. Had observed a similar case with a similar appearance but with even lower I.Q.—*S. Brandt:* Was the urine investigated for the presence of phenylpyruvic acid? Are the biopsy findings absolutely specific for inflammation or may this finding also be a reaction of metabolic disturbance? The supposed infectious origin cannot be proved when the virus remains unknown. Dr. Brandt would also like to know how much the histological picture varies from one section of muscle to another before being convinced that repeated muscle biopsy can be employed as a criterion of the efficacy of treatment.—*Henning Andersen:* Had treated a patient with dermatomyositis for 5–6 years with cortisone and later with prednisone. Was of the opinion that treatment of polymyositis must be very prolonged. In one case of polymyositis with calcification, the calcification disappeared after treatment with ACTH for 3 weeks.—*P. Plum:* The problem is if heredity, course of the disease and the biopsy findings in these muscular diseases are connected. There appear to be many variations.—*Milfeldt:* Perivascular infiltration with lymphocytes may be present in many or all forms of muscular atrophy. Prostigmine should have been attempted intravenously or for a prolonged period. The EEG might have been of interest.—*Torben Fog:* The presence of round cells appears to be of insignificant interest as regards the diagnosis of type as it is present in many different diseases. The extent of the difference between polymyositis and progressive muscular atrophy cannot be delimited. It is, however, of value to mention the clinical picture which takes a course with pyrexia, raised blood sedimentation rate and presence of metachromic substance in abnormal quantities in the biopsy specimens. Was metachromic substance found in abnormally great quantities in the biopsies in these cases?—*Hvidt:* Tensilon administered intravenously was of no effect. The urine was not examined in view of phenylpyruvic acid amentia. The EEG was normal in both patients.

S. Brandt: **Experience in the Out-Patient Treatment of Epileptic Children.**

Since 1952, all children with seizures investigated in Queen Louise's Hospital for Children, Copenhagen, were followed-up after discharge from hospital in the Out-Patient Clinic for Epileptics and, if necessary, finally adjusted to antiepileptic drugs. On an average, 15 children were seen weekly on a single consultation day. The object of this examination was: 1. to adjust the child while he remains in his normal environment, 2. to find out the most favourable drug and the dosage thereof, 3. to exercise continued clinical and neurological control in view of symptomatic epilepsy and thus avoid submitting some children to air encephalography during admission, 4. to ensure regular blood control when substances are employed which may have toxic side-

effects on haematopoiesis. Frequently, a considerable number of antiepileptic preparations had to be tried. The results after two or more years of treatment and observation are reported for 100 children with verified epilepsy (41 boys and 59 girls). The diagnoses were: Symptomatic epilepsy: 16, cryptogenic non-familial epilepsy: 54 and cryptogenic (familial?) epilepsy: 30. Epilepsy had commenced prior to the age of 2 years in 30 children, prior to the age of 5 years in 37 and prior to the age of 9 years in 25. Out of 25 children suffering from pyknolepsy 22 were between the ages of 2 and 9 years when the symptoms started. The 7 children with myoclonic and akinetic epilepsy were all small when the attacks occurred. Pure absence epilepsy was frequent (25 children). Employing the frequency of seizures as a criterion of the result of treatment the following figures were obtained: 31 cases became free from seizures, 22 were apparently free from seizures (children with relatively few seizures), 19 had improved and 28 were unchanged. The changes in the EEG corresponded to the clinical course, by and large. The results were most favourable among children with pure absence epilepsy and children with symptomatic epilepsy and poorest in children with complicating mental retardation and children with severe types of seizures. Recurrence was seen in isolated children suffering from petit mal even after freedom from absences for several years.

Discussion.—*Tudvad:* In the Municipal Paediatric Department in Copenhagen a very considerable number of children are admitted annually with seizures. The usual principle is that children who exhibit the first seizure prior to the age of one year and in association with pyrexia are not further investigated while children with repeated seizures or seizures without pyrexia are investigated as thoroughly as possible. What do the neurologists think of that procedure?—*A. Kiörboe:* Emphasized that the prognosis for children treated as out-patients is exactly the same as in adults with epilepsy of relatively recent origin as approximately 50 per cent of these cases may be rendered entirely or practically entirely free from seizures. Children with pyknolepsy are, on the whole, of good intelligence. Treatment of the parents is frequently of as great importance as that of the children. Overprotection is a serious complication and may provoke seizures.—*Stubbe Teglbjerg:* Dr Brandt's presentation of the results of treatment of 100 children is of value as case reports but there are great difficulties in employing the results as norms for children with epilepsy. More than 5 per cent of all children have seizures prior to the age of 5 years. When single or only few seizures occur on cutting the teeth, pyrexia etc. these are termed tooth-cutting or pyrexial seizures etc. but these seizures do not differ principally from epileptic seizures, although very few of these children with such fits develop chronic epilepsy. In focal cerebral conditions the seizures show focal symptoms if the brain lesion is in the third of the brain which can give rise to focal symptoms. When the lesion is in the two thirds which are "silent", in the neurological sense, cryptogenic or "genuine" epileptic seizures occur but it will often be possible by means of EEG, air encephalography etc. either immediately or later to reveal the organic focal brain lesion which has released the cryptogenic seizure. The subdivision into symptomatic and cryptogenic epilepsy is, therefore, very uncertain.—*Plum:* In siblings frequently only one of the children develops pyrexial seizures. Neonatal seizures which commence on the 3rd–4th days of life have a serious prognosis.—*Brandt:* All of the children in the Out-Patient Clinic for Epilepsy were examined neurologically and electroencephalography was performed. Air encephalography was undertaken where the neurologist considered it desirable.

J. Flamand Christensen and Mogens Lund: **Benign Infantile Hypotonia.**

Sixteen children who were referred for examination at the age of 1–2 years on account of retarded static development, hypotonia and hyperflexibility were followed-up for from 2 to 4 years. Four of the cases could be classified as cerebral palsy of ataxic type and two of these improved but none were cured; in three cases cerebral palsy in the form of diplegia atonica with oligophrenia was found and the prognosis was poor. In three cases, diplegia atonica of slighter extent was found and the prognosis was good. In one case pronounced laxity of the joint capsules and connective tissue of congenital origin was found. In 5 cases no sign of cerebral or muscular changes were found. These cases improved spontaneously and were cured after 2–4 years of follow-up control. The term benign infantile hypotonia is proposed for this group which corresponds to Oppenheim's amytonia congenita and Walten's benign congenital hypotonia as the etiology is unknown and the congenital nature of the condition has not been proved.

Discussion.—*Brandt:* Pearlstein was able to improve muscle tone in children with flaccid cerebral palsy with prostigmine. The lecture reveals that Oppenheim's myatonia still exists and that the prognosis is good.

Film from the Home for Spastic Children in Søllerød: The film demonstrates the kinetics of play in normal children and in children with cerebral palsy.

H. Kreutzfeldt, Copenhagen, Denmark.

Pediatric Society of South Sweden

Meeting March 16, 1958

S. Axtrup: **1. Hereditary congenital abnormalities in elbows, knees and nails.**

This disease was described in 1909 by Wrede. It seems to have been investigated best by *Wildervanck* (1950), who has followed five generations of a family and found the disease in 22 of its members. It is inherited dominantly and is not sex-linked. The following typical symptoms are reported. A. Luxation of the capitulum radii. B. Luxation, lack or hypoplasia of the patellae. C. Changes in the finger nails. Other skeletal anomalies are underdeveloped heads of the humerus, big toes with ankylosed joints and crooked little fingers.

Fourteen-year-old boy, one of three siblings. One sister, mother, maternal grandfather, four of his siblings and his father have according to the preliminary family investigation suffered from the same disease. The patient exhibits the skeletal changes in the elbow joints including the luxation of the head of the radius typical of the disease. He has small hypoplastic patellae and the typical changes in the nails.

2. Dyplasia epiphysialis multiplex.

The disease is characterized by dwarfism, short fingers and signs of disturbance in the epiphyses. It has been known for a long time but has gone under varying names. It received its present name from the work of *Fairbanks* (1947). The cause of the disease is unknown. The epiphyses are calcified late and exceedingly irregularly. Due to the body weight the epiphyses are gradually deformed. The disease usually appears

first in children and young people, but it exists from birth. The initial symptom is difficulty in walking. The disease seems to be hereditary, but it may also occur sporadically. Both sexes are stricken with the same frequency.

Five-year-old girl, only child, with healthy parents. No joint diseases in the family. At 8 months of age after a febrile period she began to have tenderness in the left knee joint. Roentgenography revealed a pea-sized focus, which was interpreted as an osteitis. Roentgenographic control showed regression and after about 3 months the changes appeared to have healed. She returned at 4 years of age. She had a rolling and wobbly gait, and she had complained for 3 months over tenderness in one shoulder. On examination changes typical of d. e. m. were found in the shoulders and hip joints, where the heads of the joints on both sides are markedly deformed with flattened and irregular epiphyses. (Re-examination of the pictures taken when the girl was 6 months old revealed that the heads of the joints exhibited distinct epiphysial changes already at that time.) The distal epiphysial ossification center of the left humerus is deformed and has a reduced calcium content. The anterior part of the 7th rib on the right side is thinner and broader. The pelvis shows bladder-shaped attenuations in the region of the right sacro-iliac joint. In the right parietal bone there is a pea-sized defect. Blood examinations, including calcium, phosphorus and phosphatases, are normal. The motility of the patient in relation to the grave roentgenographic findings is surprisingly good. Height 101.5 cm. Weight 15.4 kg. (Average height for this age is 110 cm).

3. Hypertelorism.

Two-year-old girl. No hereditary for hypertelorism. Normal development. The girl is alert. She has a marked distance between the eyes and a distinct broadening of the nasal root. She has syndactylism.

Ingrid Gamstorp: **Juvenile myasthenia gravis.**

Two cases of juvenile myasthenia gravis from the Pediatric Clinic, Lund, are described. The first patient is a girl who at 11 years of age developed her first symptoms: weakness, ptosis, ophthalmoplegia and difficulties in swallowing and speech. She began half a year later to take neostigmin 15 mg × 3. The disease progressed and in spite of increasing doses of neostigmin, mestinon and mytelase she has during the past winter had several attacks of threatening suffocation together with pneumonia and even without any signs of infection. She is a typical example of a grave juvenile myasthenia with a probably bad prognosis.—The second patient is a boy in whom the disease started at 5 years of age with unilateral ptosis, which 2 months later became bilateral. During the following 18 months the patient developed an almost complete ophthalmoplegia externa, slight paresis of the left lower facial muscles and of the pharyngeal muscles. After that the patient improved spontaneously and without any measures he is now almost symptom-free. There has never been general weakness and neostigmin has had no effect. Tensilon 0.2 ml i.m., however, gave a slight but obvious improvement. Testing with d-tubocurarine i.v. revealed an increased sensitivity to this drug, as half the dose expected to give a slight reaction induced a strong one in this patient. Electromyographic investigation of the left orbicularis oris showed slight signs of myopathy. Histologic examination of a biopsy specimen from an eye muscle was normal. This boy has presumably myasthenia gravis, now in spontaneous remission, but the diagnosis is not proved and will never be so if the patient in the future remains symptom-free.

Carl R. Grunewald: **Sleep treatment of children with psychic disorders.**

Twenty-seven children, ranging in age from 6 to 17 years, have been treated with the sleep cure at the Psychiatric Clinic for Children in Kristianstad. The method has been worked out by W. Silferskiöld. The patient is given Diemalnatrium and Amytal for 7 days and is kept somnolent but should be awake a few hours a day. In 17 of the cases the indication has been a neurotic condition of a depressive sort with varying symptoms and in 4 cases obsessional neurosis. All have been considerably sick, and for a long time often been subjected to other therapeutic measures. Three advantages of the sleep cure may be stressed: 1. The behavior and verbal communication of the child during the cure is often of considerable *diagnostic significance*. 2. The child acquires a strong *emotional contact*, which forms a favorable starting point for subsequent psychotherapy. 3. *Somatic effect on the central nervous system*. This may be conceived as a breaking down of conditoned reflexes at different levels. This is in agreement with the experience that the effect of the sleep treatment stands in a certain relation to how strongly the adaptive psychic condition has been fixed. The results in the stated indications are exceedingly favorable. They are better and are obtained more quickly than with psychotherapy alone, presupposing however contact with parents and reconditioning of the environment as in other cases. Especially noteworthy is the marked improvement of the 4 cases of obsessive neurosis. Two of these had among other symptoms pronounced tics and 3 had compulsive symptoms. The period of observation was ½ to 1½ years. No somatic complications have arisen.

Ulf Magnusson: **Anesthesia of the mucous membrane as an aid in the treatment of pertussis.**

In infants pertussis causes at time prolonged apneal states. These can lead to irreparable brain injuries and can be fatal. Many methods have been tried for the purpose of relieving or preventing these apneal states. Among other things attempts have been carried out to make the tracheal and laryngeal membrane less irritable by aspirating mucus from these regions or by aerosol treatment with adstringent agents, for example with synthetic antihistamines. Prevention of apneal attacks has also been attempted by the administration of a paravertebral cervical anesthesia. During the past year at the Pediatric Department of Kristianstad Central Hospital two infants with severe pertussis have been treated. Both children had apneal attacks, which we considered to be fatally dangerous. Therefore we began a spray-treatment with a solution composed of a local anesthetic (Tetracain 2 %) and an adstringent agent (Cyclosan = ½% cyclopentadrine chloride) in the proportions 2 parts Tetracain and 1 part Cyclosan. One or two sprayings down into the throat relieved an attack, and if the treatment was repeated every three hours, the patient was freed from the apneal attacks and the coughing attacks decreased considerably. Both children could be discharged completely unaffected. They had been treated at the same time with antibiotics, etc. During the treatment they had to be fed by a feeding tube on account of pharyngeal anesthesia. The method is worth trying in severe pertussis with prolonged apneal states. The toxic Tetracain should, however, be exchanged for some other local anesthetic, e.g., Novesin.

. . Axtrup: **Complications in feeding with Milkotal.**

The chemical composition of Milkotal (Kabi) corresponds closely to that of breast milk. At the Pediatric Department of Kristianstad Central Hospital Milkotal was

tested on four infants with difficult eczema.—*Case 1.* 15-month-old girl. In the beginning the girl had been given Citrido (citric acid milk) and later ordinary baby food. This diet was supplemented with 100 g of Milkotal at each meal. The girl took the preparation with the greatest distaste. She began to vomit, and after a few days she lost her appetite completely. She appeared apathetic and tired, and her eczema became considerably worse. The Milkotal supplement was discontinued, and a few days later the patient was again alert and ate with a good appetite.—*Case 2.* 11-month-old boy. Diet: Citrido milk and gradual change to baby food. Milkotal was given as a supplement. The child lost his appetite completely and began to vomit. After a few days he vomited violently in connection with the meals. The eczema became obviously worse, and at the same time he began to show signs of asthmatic bronchitis. The Milkotal was discontinued, and a few days later he was as usual without vomiting.—*Case 3.* 6-month-old boy. Diet: Citrido milk. Already at the first, but especially at the second Milkotal meal the patient developed general urticaria and became pale and tired. The Milkotal was discontinued and the Citrido milk resumed. The troubles disappeared rapidly. Two days later Milkotal was tried again. During the feeding the patient suddenly became strongly affected, flaccid and palely cyanotic, had intense dyspnoea with prolonged, groaning expiration. After adrenalin he recovered, and the attack then rapidly receded. He was quite well on the ordinary Citrido mixture.—*Case 4.* 4-month-old girl. Diet: Citrido milk, changed one week after admittance to Milkotal. Immediately after the first Milkotal meal the patient suddenly became palely cyanotic, flaccid, developed a weak pulse and intensive asthmatic dyspnoea. The patient was treated with adrenalin injections, and the ventricle was evacuated. After a short time the patient improved and then recovered rapidly. Four hours later she was fed with Citrido milk without any reactions.

The Milkotal preparation which we used was later examined by A. O. Kabi and found to be beyond criticism. It has been tested in normal infant feeding under careful clinical control, even with infants suffering from eczema, without the occurrence of any complications.

PER SELANDER, Malmö, Sweden.

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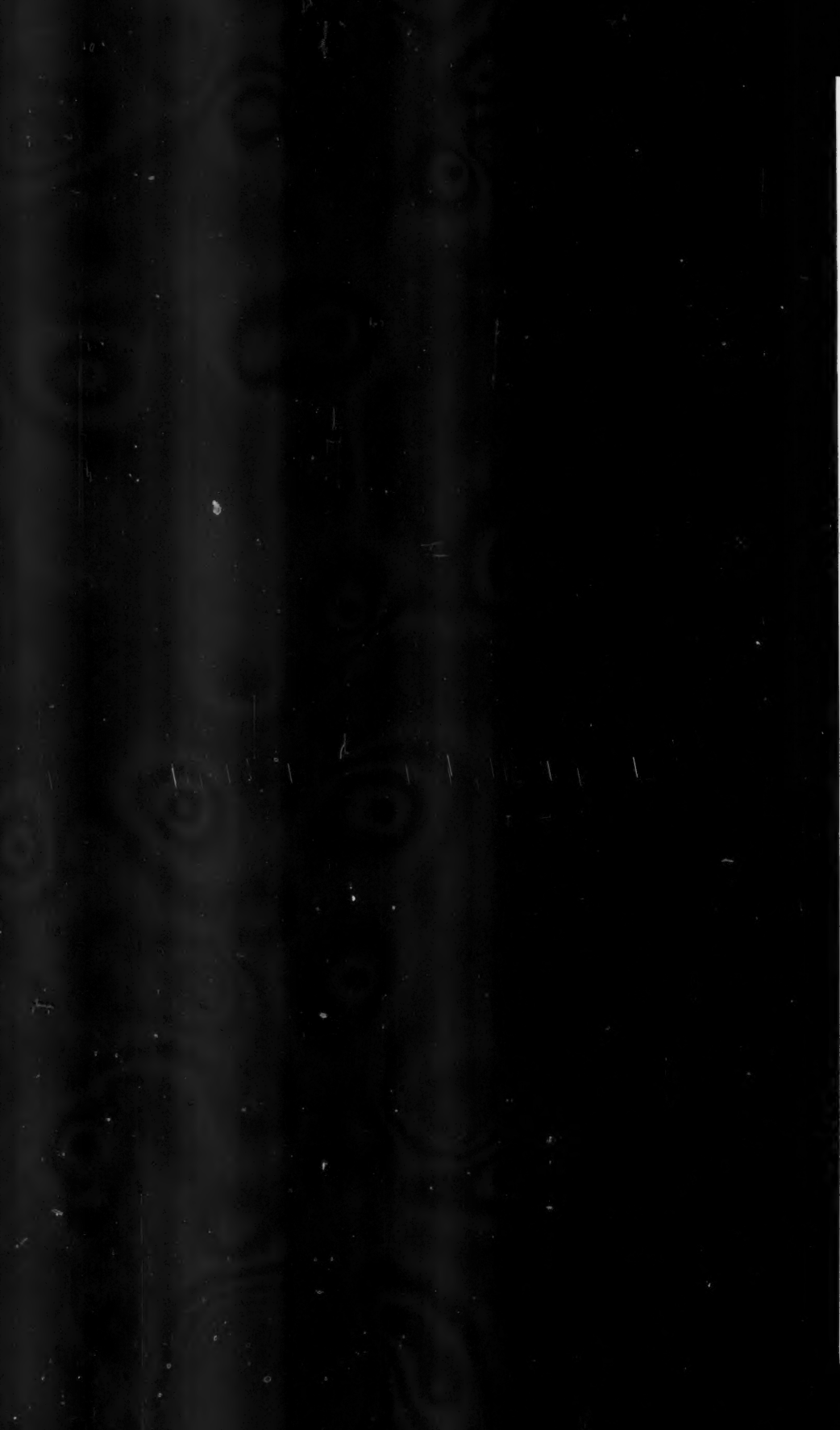

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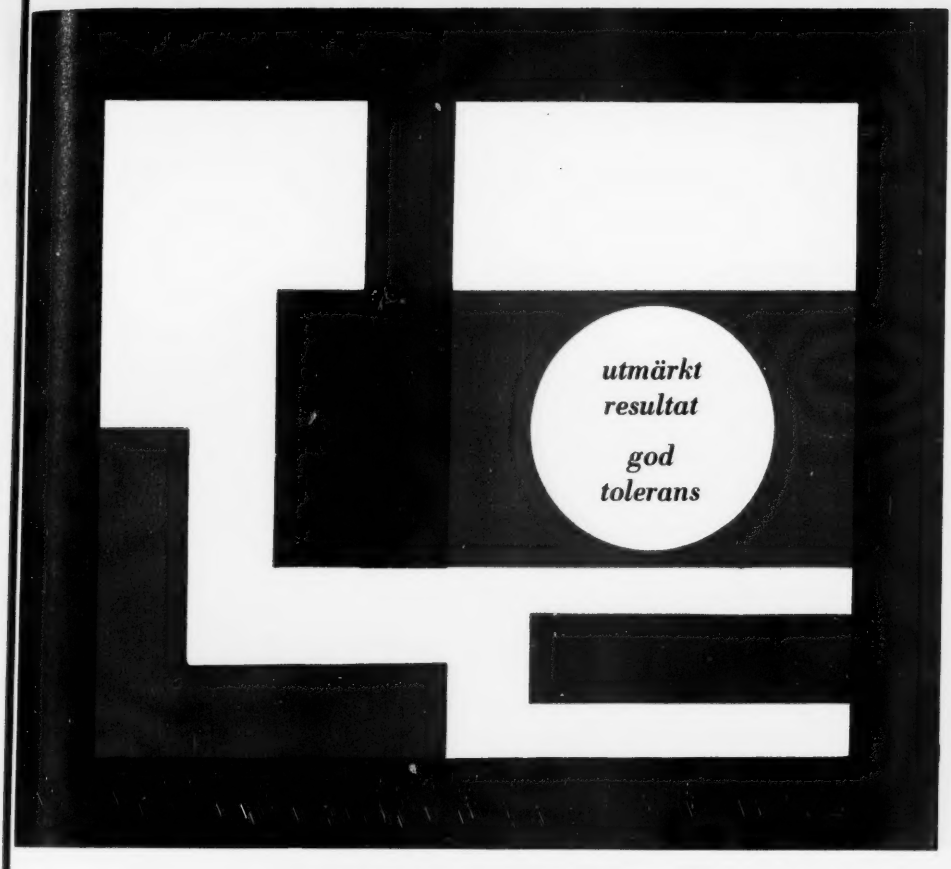

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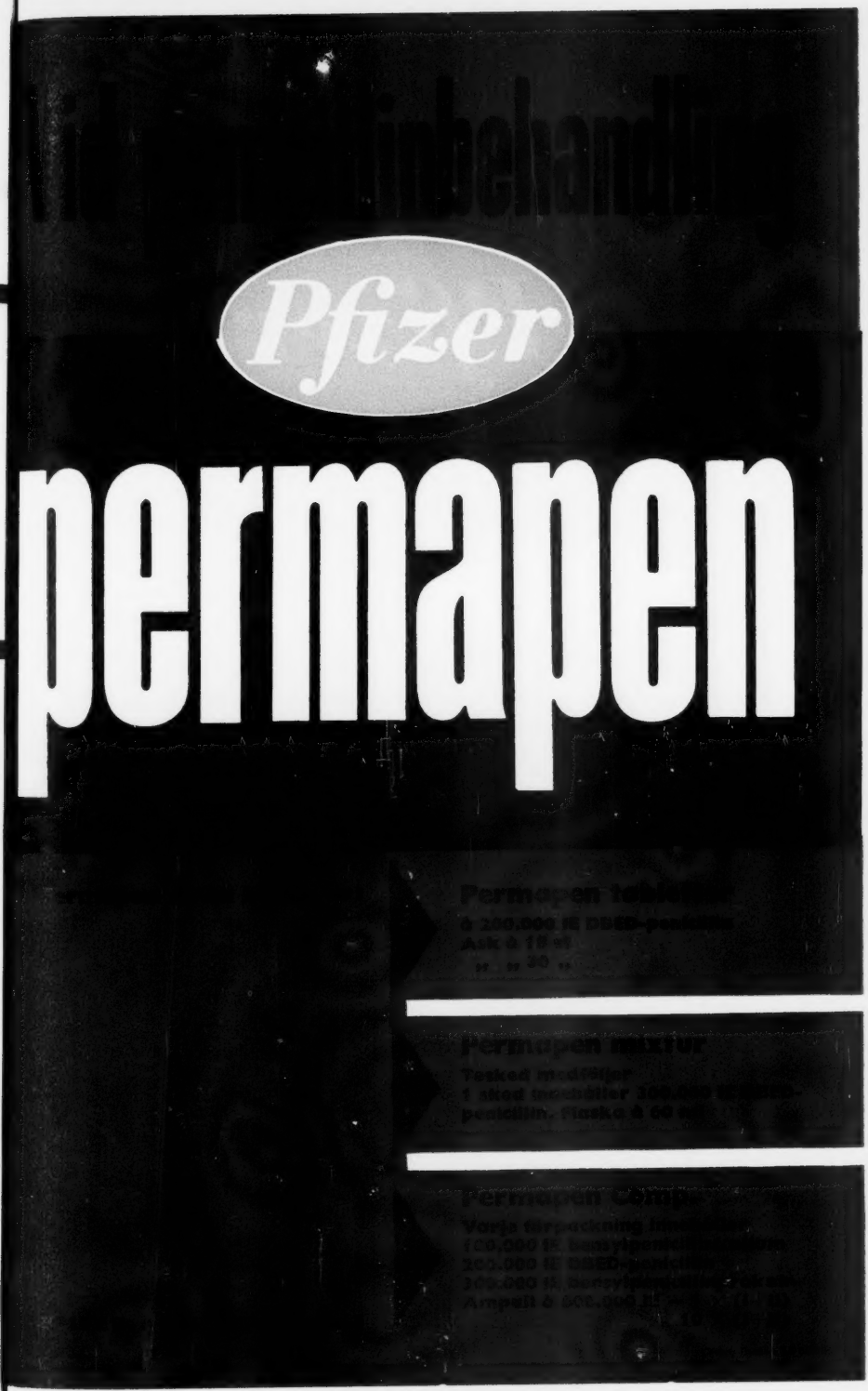
Författare	Antal pat.	Förbättring	Ingen förbättring	Biverkningar
Andelman	**50**	**48**	**2**	**0**
Cornbleet	**50**	**50**	**0**	**0**
Hutner	**291**	**290**	**1**	**allergisk reaktion, 1 fall**
Lubowe	**44**	**43**	**1**	**allergisk reaktion, 1 fall**
Robinson	**575**	**530**	**45**	**0**
Welsh	**232**	**231**	**1**	**lokal irritation, 5 fall**
Totalt	**1.242**	**1.192 (96 %)**	**50**	

De sjukdomar, som förekommer i större antal är de som vanligen förekommer i dermatologisk praxis, nämligen:

Atopisk dermatit	442 fall
Kontaktdermatit eller dermatitis venenata	221 „
Eksematös dermatit	100 „
Pruritus ani eller vulvae	91 „
Seborrhoisk dermatit	74 „
Stasdermatit	56 „
Follikulit	40 „
Neurodermatit	33 „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Vid penicillinbehandling

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DBED-penicillin

Permapen-serien består av:

Permapen tabletter
à 200.000 IE DBED-penicillin
Ask à 18 st
„ „ 30 „

Permapen mixtur
Tesked medföljer
1 sked innehåller 300.000 IE DBED-penicillin. Flaska à 60 ml

Permapen Comp.
Varje förpackning innehåller
100.000 IE bensylpenicillinkalium
200.000 IE DBED-penicillin
300.000 IE bensylpenicillinprokain
Ampull à 600.000 IE — 1 × (I+II)
10 × (I+II)

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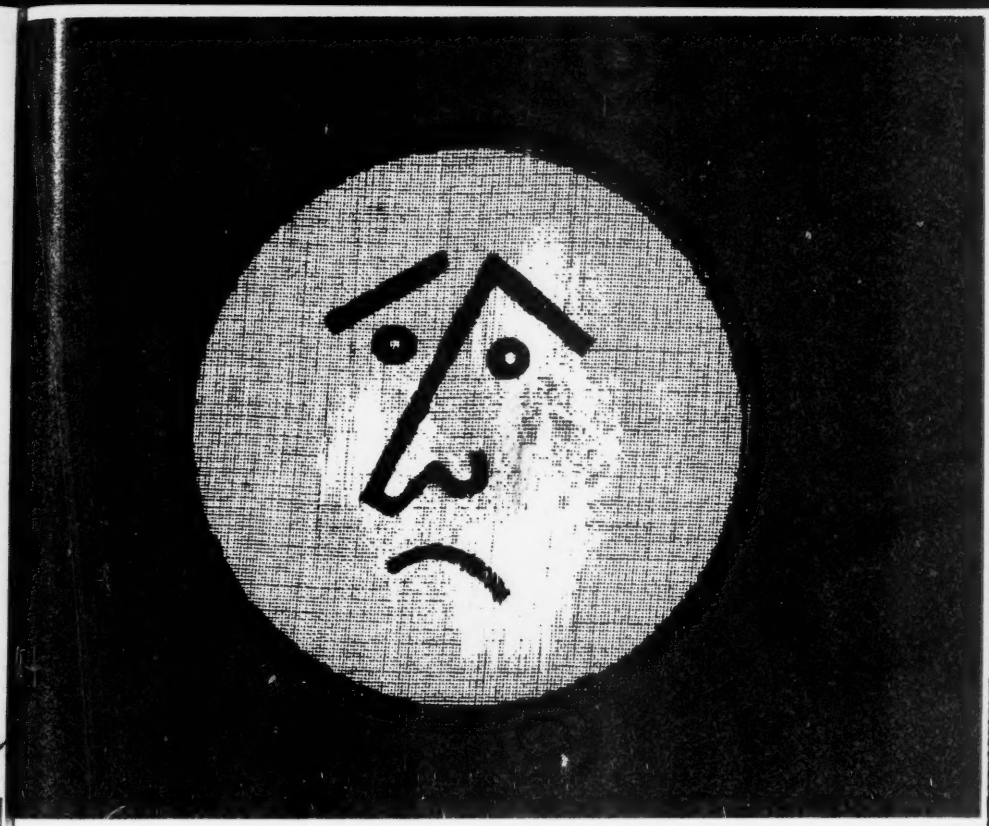

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Försök med koncentrationen 0,5 % har visat, att även denna ger en fullt användbar salva, lämplig för många fall, särskilt sådana med ytliga utbredda symtom, t. ex. vissa kontakteksem, underbenseksem, Prurigo Besnier hos småbarn. Bo Bäfverstedt, Sv. Läkartidn. No. 34, 1955.

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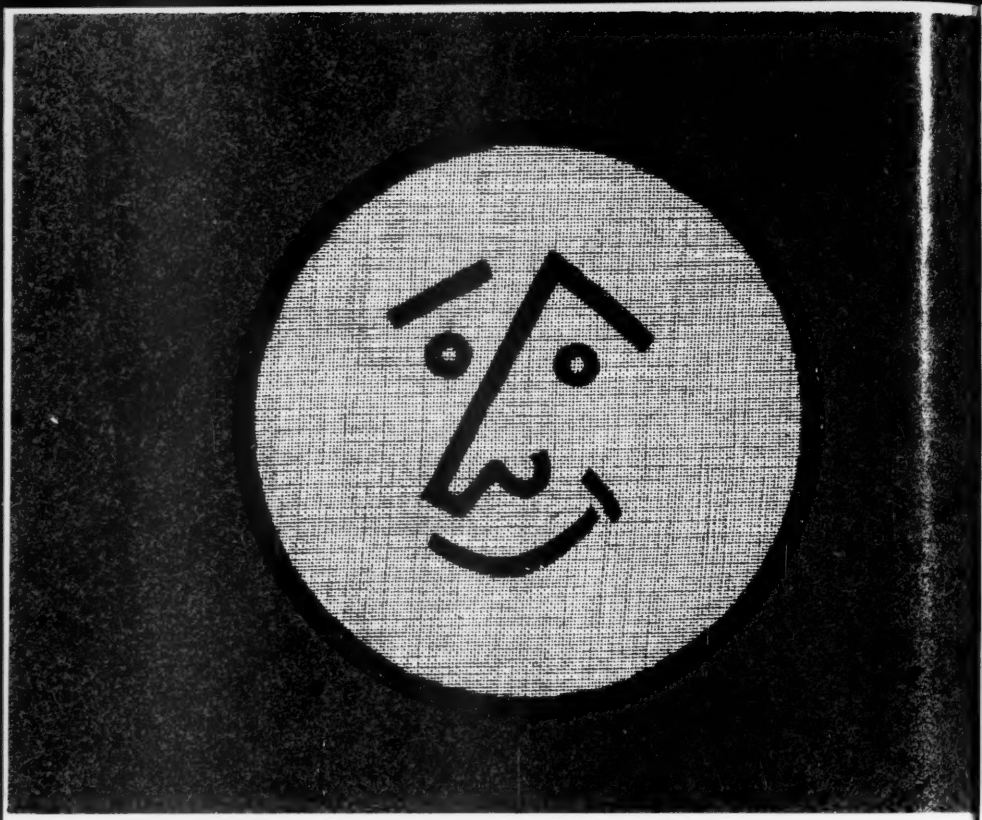

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